A STUDY OF SERUM MAGNESIUM LEVELS AT PRESENTATION OF ACUTE MYOCARDIAL INFARCTION

Dissertation submitted to

THE TAMIL NADU DR.M.G.R. MEDICAL UNIVERSITY

CHENNAI -TAMIL NADU

In partial fulfilment for the Degree of

DOCTOR OF MEDICINE
BRANCH I – M.D., GENERAL MEDICINE

APRIL – 2015

DEPARTMENT OF MEDICINE
TIRUNELVELI MEDICAL COLLEGE HOSPITAL
TIRUNELVELI- 627011
TAMIL NADU

CERTIFICATE

This is to certify that the Dissertation entitled **"A STUDY OF SERUM MAGNESIUM LEVELS AT PRESENTATION OF ACUTE MYOCARDIAL INFARCTION"** submitted by **Dr.RAEEZ MOHAMMED BASHEER** to The Tamilnadu Dr. M.G.R. Medical University, Chennai, in partial fulfilment for the award of M.D.(Branch-I)General Medicine Examination to be held on April 2015 is a bonafide work carried out by him under my guidance and supervision. This dissertation partially or fully has not been submitted for any other degree or diploma of this university or other.

Prof. Dr. J.M.RAVICHANDRAN EDWIN, M.D.,D.M.,
Professor and HOD of Cardiology
Department of Medicine
Tirunelveli Medical College
Tirunelveli-627011

Prof. Dr.VAIRAMUTHURAJU, M.D
Professor and HOD
Department of Medicine
Tirunelveli Medical College
Tirunelveli-627011

The Dean,
Tirunelveli Medical College,
Tirunelveli – 627 011.

TIRUNELVELI MEDICAL COLLEGE

INSTITUTIONAL RESEARCH ETHICS COMMITTEE
TIRUNELVELI, STATE OF TAMILNADU, SOUTH INDIA PIN 627011
91-462-2572733-EXT; 91-462-2572944; 91-462-2579785; 91-462-2572611-16
online@tvmc.ac.in, tirec@tvmc.ac.in; www.tvmc.ac.in

CERTIFICATE OF REGISTRATION & APPROVAL OF THE TIREC REF NO: 349/GM/2013/29.03.13

PROTOCOL TITLE: A Study of Serum Magnesium Levels at Presentation of Acute Myocardial Infarction

NAME OF PRINCIPAL INVESTIGATOR: Dr.Raeez Mohammed Basheer

DESIGNATION OF PRINCIPAL INVESTIGATOR: Post Graduate Resident

DEPARTMENT & INSTITUTION: Department of General Medicine, Tirunelveli Medical College

Dear Dr Dr.Raeez Mohammed Basheer, *the Tirunelveli Medical College Institutional Ethics Committee (TIREC) reviewed and discussed your application during the IEC meeting held on* 29.03.2013.

THE FOLLOWING DOCUMENTS WERE REVIEWED AND APPROVED

1.	TIREC Application Form	☑
2.	Study Protocol	☑
3.	Department Research Committee Approval	☑
4.	Patient Information Document and Consent Form in English and Vernacular Language	☑
5.	Investigator's Brochure	☑
6.	Proposed Methods for Patient Accrual Proposed	☑
7.	Curriculum Vitae of the Principal Investigator	☑
8.	Insurance /Compensation Policy	☐
9.	Investigator's Agreement with Sponsor	☐
10.	Investigator's Undertaking	☑
11.	DCGI/DGFT approval	☐
12.	Clinical Trial Agreement (CTA)	☐
13.	Memorandum of Understanding (MOU)/Material Transfer Agreement (MTA)	☑
14.	Clinical Trials Registry-India (CTRI) Registration	☐

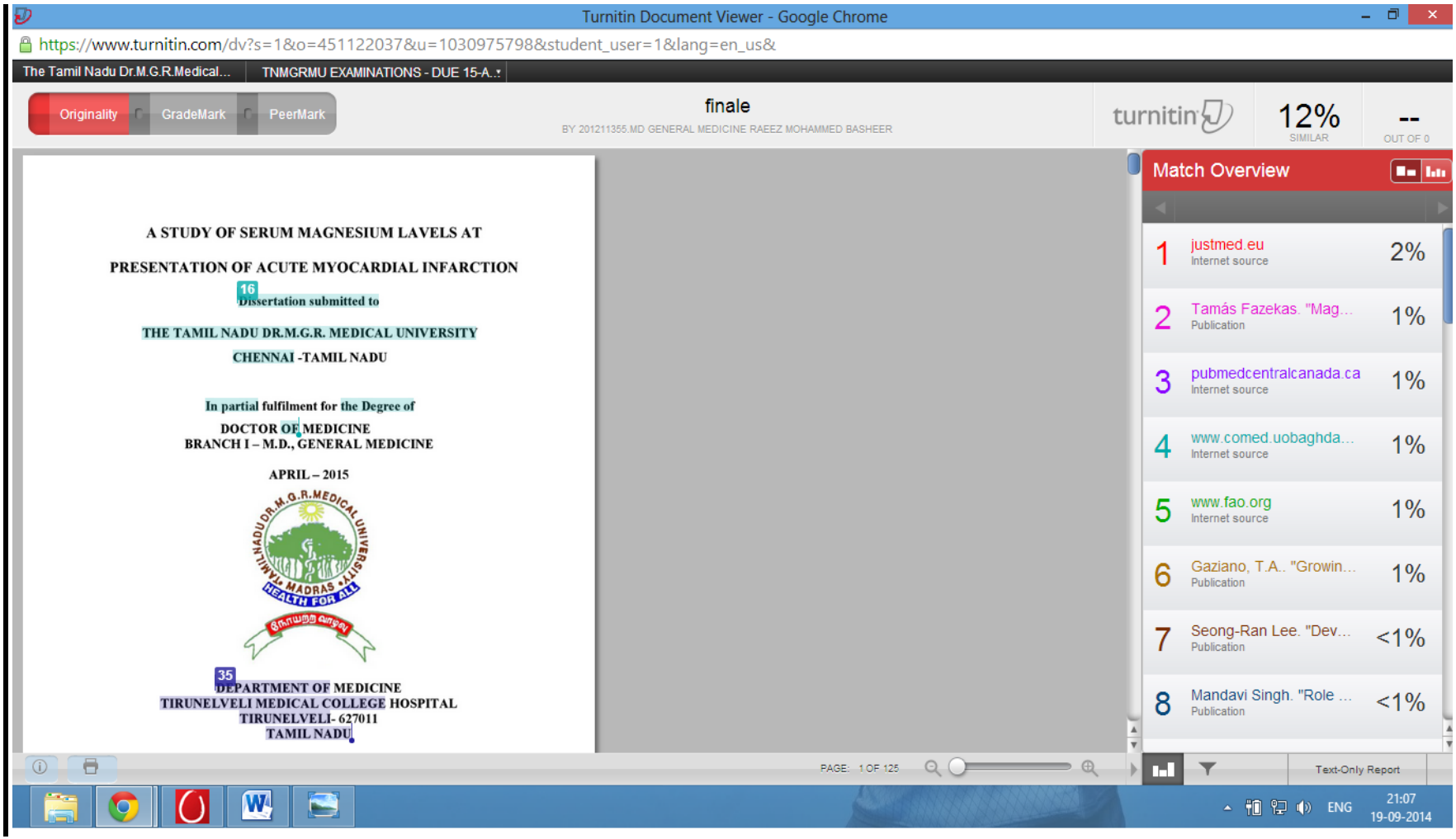
THE PROTOCOL IS APPROVED IN ITS PRESENTED FORM ON THE FOLLOWING CONDITIONS

1. The approval is valid for a period of 2 year/s or duration of project whichever is later
2. The date of commencement of study should be informed
3. A written request should be submitted 3weeks before for renewal / extension of the validity
4. An annual status report should be submitted.
5. The TIREC will monitor the study
6. At the time of PI's retirement/leaving the institute, the study responsibility should be transferred to a person cleared by HOD
7. The PI should report to TIREC within 7 days of the occurrence of the SAE. If the SAE is Death, the Bioethics Cell should receive the SAE reporting form within 24 hours of the occurrence.
8. In the events of any protocol amendments, TIREC must be informed and the amendments should be highlighted in clear terms as follows:
   a. The exact alteration/amendment should be specified and indicated where the amendment occurred in the original project. (Page no. Clause no. etc.)
   b. The PI must comment how proposed amendment will affect the ongoing trial. Alteration in the budgetary status, staff requirement should be clearly indicated and the revised budget form should be submitted.
   c. If the amendments require a change in the consent form, the copy of revised Consent Form should be submitted to Ethics Committee for approval. If the amendment demands a re-look at the toxicity or side effects to patients, the same should be documented.
   d. If there are any amendments in the trial design, these must be incorporated in the protocol, and other study documents. These revised documents should be submitted for approval of the IEC, only then can they be implemented.
   e. Approval for amendment changes must be obtained prior to implementation of changes.
   f. The amendment is unlikely to be approved by the IEC unless all the above information is provided.
   g. Any deviation/violation/waiver in the protocol must be informed

STANDS APPROVED UNDER SEAL

Dr.K.Shantaraman MD
Registrar, TIREC
Tirunelveli Medical College, Tirunelveli – 627011
State of Tamilnadu, South India

Dr.V.Ramasubramanian MD DM
Member Secretary, TIREC
Tirunelveli Medical College, Tirunelveli – 627011
State of Tamilnadu, South India


Turnitin Document Viewer - Google Chrome
https://www.turnitin.com/dv?s=1&o=451122037&u=1030975798&student_user=1&lang=en_us&
The Tamil Nadu Dr.M.G.R.Medical...
TNMGRMU EXAMINATIONS - DUE 15-A..
Originality
GradeMark
PeerMark
finale
BY 201211355.MD GENERAL MEDICINE RAEEZ MOHAMMED BASHEER
turnitin
12%
SIMILAR
--
OUT OF 0
A STUDY OF SERUM MAGNESIUM LAVELS AT
PRESENTATION OF ACUTE MYOCARDIAL INFARCTION
Dissertation submitted to
THE TAMIL NADU DR.M.G.R. MEDICAL UNIVERSITY
CHENNAI -TAMIL NADU
In partial fulfilment for the Degree of
DOCTOR OF MEDICINE
BRANCH I – M.D., GENERAL MEDICINE
APRIL – 2015
DEPARTMENT OF MEDICINE
TIRUNELVELI MEDICAL COLLEGE HOSPITAL
TIRUNELVELI- 627011
TAMIL NADU
Match Overview
1 justmed.eu Internet source 2%
2 Tamás Fazekas. "Mag... Publication 1%
3 pubmedcentralcanada.ca Internet source 1%
4 www.comed.uobaghda... Internet source 1%
5 www.fao.org Internet source 1%
6 Gaziano, T.A.. "Growin... Publication 1%
7 Seong-Ran Lee. "Dev... Publication <1%
8 Mandavi Singh. "Role ... Publication <1%
PAGE: 1 OF 125
Text-Only Report
ENG
21:07
19-09-2014

DECLARATION

I, **Dr. RAEEZ MOHAMMED BASHEER** declare that I carried out this work on **"STUDY OF SERUM MAGNESIUM LEVELS AT PRESENTATION OF ACUTE MYOCARDIAL INFARCTION"**, at department of general medicine, Tirunelveli Medical College and hospital during the period of August 2013 to September 2014. I also declare that this bonafide work or a part of this work was not submitted by me or any others for any award, degree, and diploma to any university, board either in India or abroad. This is submitted to the Tamilnadu Dr. M.G.R. Medical University, Chennai in partial fulfilment of the rules and regulation for the M.D Degree examination in General medicine.

Tirunelveli Medical College, DR. RAEEZ MOHAMMED BASHEER

Tirunelveli.

Date:

ACKNOWLEDGEMENT

This dissertation would not have been possible without the guidance and help of several individuals who have contributed and extended their valuable assistance in the preparation and completion of the study.

I express my sincere thanks to the Head od Department Dr. Vairamuthuraju M.D for his constant support throughout this period.

I sincerely thank my unit chief Dr.S Alagesan M.D, D.M and my former unit chief Dr. S.S Nazar for their constant guidance.

I would also like to thank Dr Thulasiraman M.S, Dean of Tirunelveli Medical College for giving me permission to conduct this study.

I am sincerely indebted to Professor Dr.Ravichandran Edwin M.D, D.M for his valuable advice and guidance throughout the study without which this study would not have happened.

I thank my assistant professors, Dr.Prince Prabhakaran M.D, Dr. T.Grashia M.D, Dr Tirulokachander M.D, Dr Rajesh Babu M.D, Dr. S.M Shavana M.D for their steadfast encouragement for completing this dissertation.

Also I am thankful to the department of Cardiology and Biochemistry for their unparalleled help and cooperation.

INDEX

A STUDY OF SERUM MAGNESIUM LEVELS AT PRESENTATION OF ACUTE MYOCARDIAL INFARCTION

Abstract

Background: According to many studies, acute myocardial infarction is associated with an increased incidence of hypomagnesemia.This may contribute to increase in the incidence of arrhythmias and complications, during the early period of acute MI.

Aims: To find out the prevalence of hypomagnesemia in the study population, and also to compare the mean magnesium levels in the study population and the control population. We will also see if the incidence of complications are higher in the hypomagnesemic patients

Materials and methods: 70 patients who presented with acute MI in Tirunelveli Medical College hospital ICCU, who did not fit into the exclusion criteria were taken as the study population. The control group had 30 participants. The serum magnesium levels were measured using the colorimetric method.

Results: Out of the 70 cases only one patient had hypomagnesemia.(1.43%). This was not significant He did not develop any complications. The mean

magnesium levels of the study group (2.01mg/dl)was however significantly lower than that of the control group(2.18mg/dl).((p value<0.01).

Conclusion: In this study, the prevalence of hypomagnesemia in MI patients was not significant. However the mean serum magnesium level of the study group was significantly lower than that of the control group. This study thus differs from the other similar studies conducted in the western population. The reason could be attributed to the high concentration of magnesium ions in the local ground water. Further studies must be done in Indian population to see if these results are reproducible or not.

Key words: Acute myocardial infarction, serum magnesium levels, hypomagnesemia, arrhythmias.

Introduction

Cardiovascular disease is still the most common cause of mortality and morbidity throughout the developing world. As we progress along the twenty first century, numerous technological innovations and breakthroughs has made our lives more and more easy. We are gradually beginning to realize some of the undesirable effects these events are having upon us, specifically regarding human health.

We as a species have existed on this planet for around 100,000 to 200,000 years according the evidence suggested by mitochondrial DNA mutation studies. Human beings have evolved primarily as hunter gatherers. Our bodies and metabolism are genetically built in a specific way which made us adaptable to the tough environment that existed in the Palaeolithic age or Stone Age. In those conditions, food availability was relatively low and there were frequent episodes of famine. This is to say that the human body was designed to survive these episodes by storing excess energy in the form of fat deposits, during the times in which food was relatively abundant. The breakthrough in agriculture came only around ten thousand years before. So for the huge majority of time in human history, we have

lived in times of shortage of food, rather than abundance of food. So our genetic condition has made us adaptable to food scarcity and physical activity, but is not well adapted to deal with over-nutrition and a sedentary lifestyle.

We have virtually eliminated physical activity or exercise from our lives. Physical inactivity is the most important cause of the modern lifestyle disease leading to cardiovascular mortality. Adding to this there is the problem of over-nutrition, especially of unhealthy food substances rich in saturated and trans-fatty acids, refined simple carbohydrates.

Increased work hours and academic competition, smaller nuclear families, noise pollution and all have greatly increased the stress levels, despite the conveniences offered by modern life. This transforms into organic diseases like hypertension, anxiety disorders and associated diseases which contribute to cardiovascular disease burden.

Coronary heart disease is the primary cause of cardiovascular mortality. Acute myocardial Infarction is the acute manifestation of coronary heart disease. Modern medicine has made numerous advances in managing the disease, including, fibrinolytic therapy, catheter based intervention, anti-platelet drugs, lipid lowering drugs, etc. Even with the best medical care, the in-hospital mortality of

acute myocardial infarctions stands at 2.5% to 5%. Considering the fact that acute MI is very common, the total number of lives lost is massive.

There is constant research not only to broaden our understanding of the established risk factors that affect the prognosis of acute myocardial infarction, but also to discover new prognostic indicators or risk factors. Many such factors such as C - reactive protein levels, blood uric acid levels, blood magnesium levels have been in the spotlight.

Magnesium is a very important element that plays innumerable roles in the proper functioning of the human body. It is a cofactor in many important enzymes involved in the metabolic functions of the body. It also has electrophysiological properties that affect ion transport and electrical transmission across cells, especially neurons and cardiac myocytes.

Magnesium is also used therapeutically in the treatment of seizures in eclampsia and in the treatment of Torsade des pointes which is a kind of ventricular tachycardia. It also has many adjuvant roles in similar disease conditions.

It is only reasonable to search for the importance of the role of magnesium in the pathophysiology and prognosis in acute myocardial infarction which can be arguably stated as one of the most dangerous of all the medical emergencies.

This thesis titled “A study of serum Magnesium levels at presentation of acute myocardial infarction” is a humble attempt at searching for the presence of any significant change in blood magnesium levels of acute MI patients who present at Tirunelveli Medical College Hospital for its management. Previous studies have leaned towards the presence of reduced magnesium levels in acute myocardial infarction patients. Some studies have also associated a poorer prognosis in such patients. The prophylactic use of magnesium in acute MI patients is an even more controversial topic. This study intends to see if the results obtained in the study population are similar to the previous studies or not.

The following pages start with elaborating the aims and objectives of the study followed by a brief review of the existing literature regarding cardiovascular disease, myocardial infarction, and the role of magnesium in the human body, especially the cardiovascular system. Then there is a discussion of the methods and materials used for the study before we dwell into the observations and results. There will be a detailed discussion of the findings followed by a summary. Finally we reach the conclusion of the study.

- Thank You.

Aims and Objectives

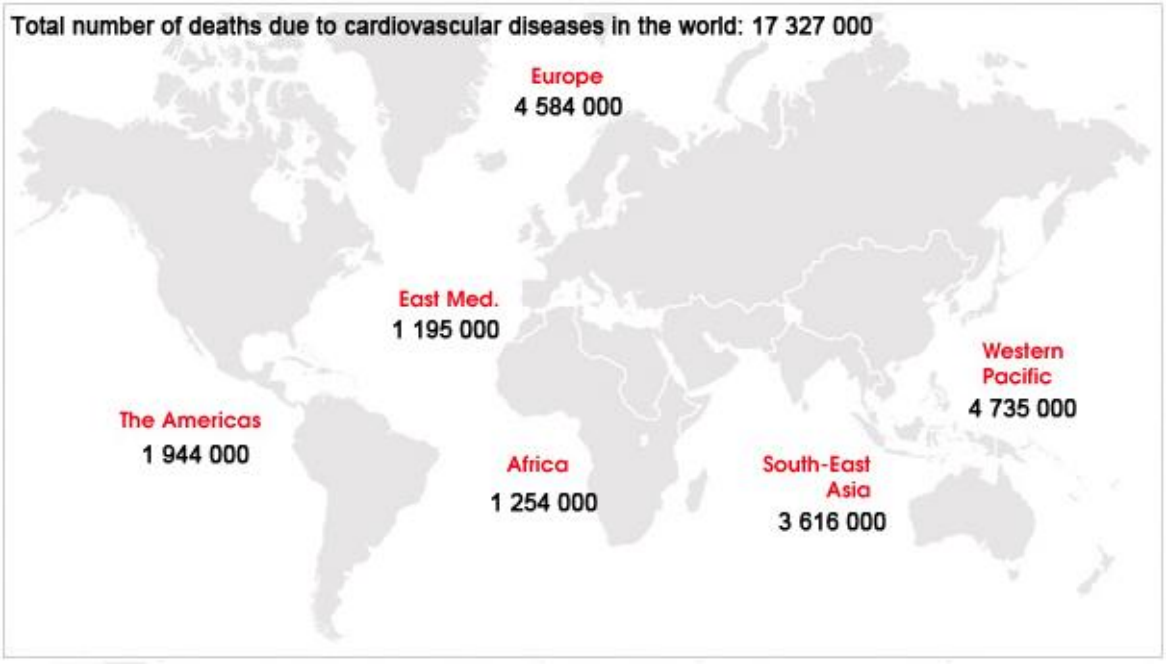
1. To estimate the prevalence of hypomagnesemia in patients who present with acute myocardial infarction and to determine its significance.

2. To find out if the hypomagnesemic patients are at a higher risk of ventricular arrhythmias or other complications.

3. To compare the mean magnesium levels between the cases and the control group and find out if the difference, if any is statistically significant.

Global burden of Cardiovascular Disease

During the last ten years, cardiovascular disease has become the single biggest cause of death all over the world. In 2004, cardiovascular disease was responsible for an estimated 17 million deaths all over the world. It accounted for thirty per cent of deaths of that year. In 2004, it was the cause for 151 million disability adjusted life years (DALY) lost. It accounted to around 14 per cent DALYs lost during that year. (1).This pattern is seen in high income countries, middle income countries and low income countries regardless. The rates of cardiovascular disease are increasing. It is not only increasing, but also accelerating.



Shifting of the burden

Cardiovascular disease is the leading cause of deaths in all the developing regions. The exception is sub-Saharan Africa. Even in sub Saharan Africa, it is the leading cause of deaths in individuals more than 45 years of age. This busts the myth that cardiovascular disease is a disease of affluent societies. Low and middle income countries are also bearing the burden. In fact more and more burden is shifting to the middle and low income countries. Between the years 1900 to2001, the deaths caused by cardiovascular disease in low and middle income countries sincreased from 26% to 28%.

Current Worldwide Distribution of Cardiovascular Disease

High-Income Countries

940 million people currently inhabit the high income countries. This comes to around fifteen per cent of the world population. They consist of the United States of America, Canada, Australia, New Zealand, Japan, and many countries of the European Union.

Here, there is overall increase in cardiovascular disease burden. The good news is that the age adjusted death rates for cardiovascular diseases are decreasing.

This is due to both primary and secondary prevention. The average age of death from CVD continues to increase.

Low and middle- Income countries.

There are six regions that make up the low and middle-income countries. There is considerable variability in the distribution of cardiovascular disease between these regions. Here the prevalence of cardiovascular disease is increasing. The important thing to consider is that the age adjusted mortality is increasing. That means that coronary heart disease affects a younger population.

These people constitute the workforce and thus it further hinders economic development in these countries. The lower socioeconomic strata are more vulnerable as they are least likely to apply health practices and to avail advanced treatments.

South Asia Including India

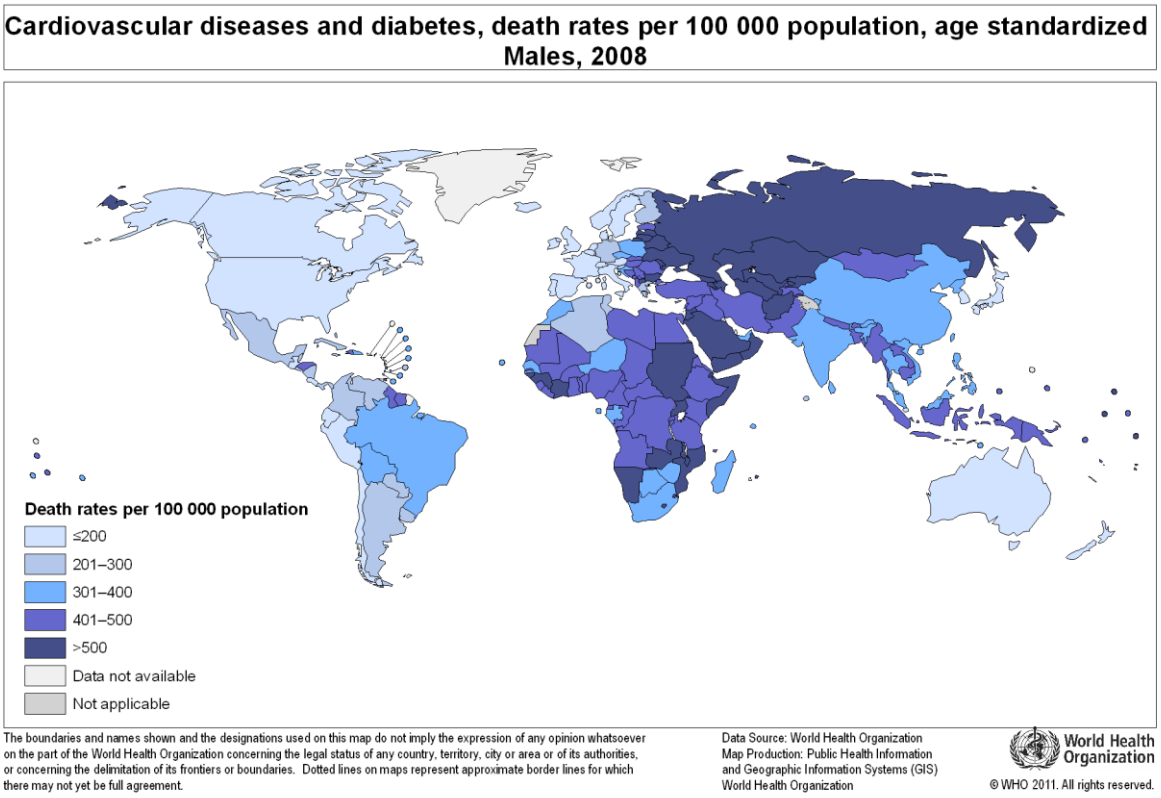
It is one of the most densely populated regions. It contains 20% of the world population. This accounts to around 1.4 billion residents. India is the largest country in this region. It is the home to more than seventy five per cent of the regions inhabitants.

Cardiovascular diseases accounted twenty five per cent of all the deaths in the region. Communicable diseases lead to 43% of all the deaths in this region, by comparison. (2)

The deaths from coronary heart disease in India is increasing.. Coronary heart disease rose from 1.17 million to 1.59 million over the previous decade.

In India alone, 31.8 million people are lining with coronary heart disease.(27) This is a tenfold increase, when compared the condition that existed 40 years ago. Women are more likely to develop cardiovascular disease in India.(39). A new study found out that the prevalence in men was 6% and the prevalence in women was 9%.

Here there is an increased use of tobacco products among the people os lower socioeconomic status, leading to a higher burden of cardiovascular disease in them. In India, 52% of deaths due to cardiovascular disease occur in individuals below 70 years of age. This is a considerable burden on working age citizens.



Risk Factors

Hypertension

Elevated Systemic blood pressure is an indicator of the transition in epidemiology. As the population becomes more and more industrialized, the mean blood pressure of the population increases. This is also true when the people move from rural to urban settings. There is a high rate of undetected and untreated hypertension in the developing countries. This is a major concern. This is true especially in Asia, this maybe the cause for high prevalence of haemorrhagic stroke.

Worldwide, around 62% of strokes and 49% of coronary heart disease are undoubtedly attributable to a sub-optimal blood pressure, i.e. more than 115 mm Hg. This accounts for more than 7 million deaths annually.

Tobacco

Tobacco use is the most preventable cause of death in the entire world. Over 1.3 billion people worldwide are consumers of tobacco. More than 1 billion people smoke. The others use oral tobacco or nasal tobacco. More than 80% of tobacco use occurs in low and middle income countries. If the current trend of tobacco use continues, there will be more than 1 billion deaths in the world during the twenty first century. Smoking related CHD deaths totaled 360,000 in 2000. There were 200,000 cerebrovascular deaths due to smoking on the same year. (3)

Second hand smoke also is now well established as a significant cause of coronary heart disease. There is a 1.3 fold increased risk of coronary heart disease following second hand smoking.

Lipids

Worldwide, increased levels of blood cholesterol, cause around 56 per cent of ischemic heart disease and 18 eighteen per cent of strokes. This amounts to 4.4 million deaths in one year. Unfortunately the data on cholesterol levels is very limited in most of the developing countries. In high-income countries, the mean

level of cholesterol is gradually falling as a result of widespread use of medications. In low and middle income countries there is wide variation in cholesterol levels.

As countries experience movement through the epidemiological transit, the mean population blood cholesterol levels typically increase. There is a very clear role played by the changes accompanying urbanization. This is evidenced by the fact that, the blood cholesterol levels are higher in urban residents than in rural residents. This change is largely a result of increased consumption of dietary fats, mainly from animal products and processed vegetable oils, and from decreased physical activity.

Physical Inactivity

In high income countries, the widely spread prevalence of physical inactivity puts the population at a very high risk for cardiovascular consequences. In a poll conducted in 2007 found that a vast majority of adults are not following the recommended amount of exercise given in health guidelines. Current heath guidelines call for vigorous exercise for twenty minutes, 3 times a week. Or moderate exercise for at least 30 minutes, 5 or more days a week.

There is a shift from physically demanding agriculture based work and manual labour to a largely sedentary service industry. Office based work is

also increasing in the population of the developing world. There is also a change from physically demanding transportation to mechanized transportation.

Diabetes

Throughout the world, approximately One Eighty million people are affected by diabetes mellitus. The worrying fact is that this number is expected to double by the year 2030. Of the people with diabetes, around ninety per cent have type 2 diabetes. Eighty per cent of them live in low and middle income countries. In the developing countries, the age group of diabetics ranges from 45 to 64. In developed countries, the most affected individuals are more than 65 years of age.

One interesting trend is that, Asian countries are more burdened with diabetes, when compared with Europe and Central Asia or Latin America and the Caribbean regions. India and China have the largest number of diabetic patients. 32 million and 21 million respectively.(4)Asian population have a greater tendency towards visceral obesity. This may be responsible for this peculiar finding.

Obesity

Obesity is increasing throughout the entire world, especially in the developing countries. The trajectory is also steeper than those seen in developed countries. According to WHO, there are approximately 1.1 billion overweight

adults in the world. Another study claims that 23% of adults older than 20 years are overweight. 10% of them are obese (BMI>30).

Obesity is not only a problem in high income individuals. The poor are relatively more at risk for obesity as a developing country's GDP moves closer to the middle income range. Women are more affected than men in these developing countries. This is based on data from 36 developing countries.

One in ten children is currently estimated to be overweight. The number of overweight children is increasing in many countries like China, brazil, India, Mexico.

In developing countries, even if the mean cholesterol levels are falling the mean BMI is increasing at an alarming rate.

Diet

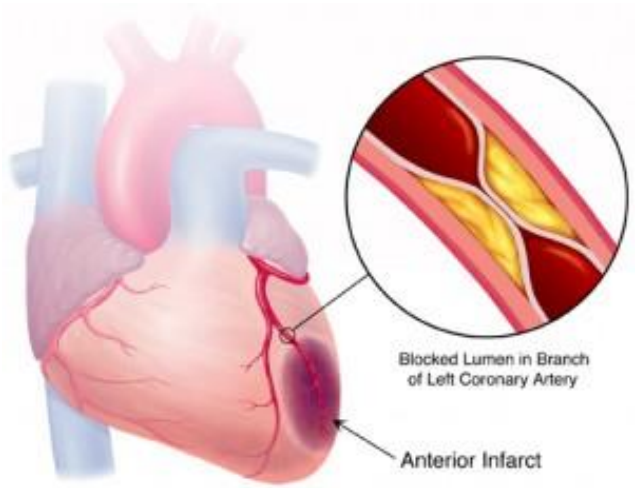
There is an increase in the consumption of processed foods, people consume larger portions of food, the regularly consume sugary drinks. There is an increase in consumption of fats and simple carbohydrates, but there is a decrease in consumption of plant based foods. Saturated fatty acid intake is increased. Hydrogenated vegetable oils are also increasingly consumed. They contain atherogenic trans-fatty acids. High intake of trans-fatty acids may lead to abdominal obesity.

Another factor is the introduction of soft drinks and other high-sugar beverages. They are associated with weight gain and increase risk for type 2 diabetes mellitus. They are an independent risk factor for coronary heart disease. (5)

Aging Population

As primary health care is improved and infectious diseases are controlled, more and more individuals live longer to reach old age. Proportion of people aged over 65 is more than one fifth in many developed countries. Elderly individuals are naturally more at risk for cardiovascular disease and more prone to suffer morbidity and mortality from the disease.

Ischemic Heart disease



Patients who are suffering from ischemic heart disease can be classified into two broad groups. One consists of patients with chronic coronary artery disease (CAD). They most commonly present with stable angina.

The second group is composed of patients with Acute Coronary syndromes (ACS). This group consists of a collection of syndromes consisting of:

1. Acute myocardial infarction with ST- segment elevation
2. Non St-segment elevation Myocardial Infarction.
3. Unstable Angina.

Unstable angina and non ST-segment elevation myocardial infarction are usually grouped together as they share similar treatment.

Incidence of ST-elevation myocardial infarction is less than that of unstable angina/non ST elevation MI. The relative incidence of NSTEMI/UA compared to

ST elevation MI appears to be increasing. More than one third of patients with unstable angina/non ST elevation MI are women. However less than one-fourth of patients with ST elevation Myocardial infarction are women.

The most important difference between the two groups is regarding the need for fibrinolysis.

Definitions

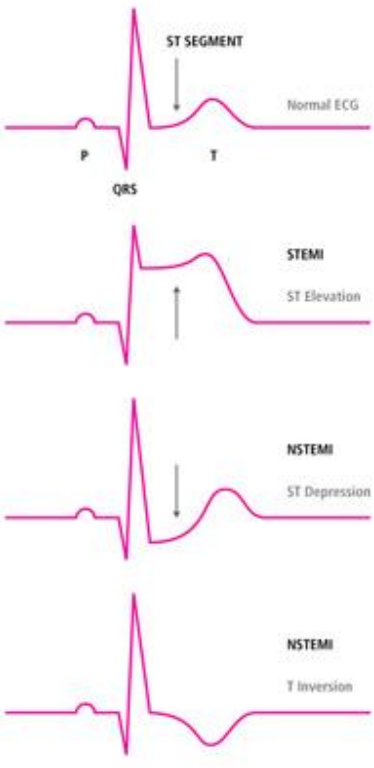
Stable angina pectoris is characterised by chest or arm discomfort that may not be always described as pain but is reproducibly associated with physical exertion and/or stress and is relieved within five to ten minutes by rest and/or sublingual administration of nitroglycerin.

Unstable angina can be defined as angina pectoris or equivalent ischemic discomfort so that it also consists of at least one of the three features:

1. It occurs during rest or with minimal physical exertion, and usually lasting for more than 10 minutes.
2. It is severe and is of new onset. (mostly within the prior 4-6 weeks)
3. It occurs with a crescendo pattern. It means that the angina is more severe, prolonged or more frequent than previously.

Non ST-segment elevation Myocardial infarction is diagnosed if a patient has the clinical features of unstable angina develops evidence of necrosis of myocardial tissue, as evidenced by elevated cardiac biomarkers.

In both unstable angina and NSTEMI the pathology includes an unstable plaque, causing sub-total occlusion of the coronary arteries. Here fibrinolysis is of limited benefit or it may even be harmful. The fibrinolytic lyses the outer fibrin layer to expose the thrombogenic core of the unstable plaque, resulting in further enlargement of the clot.



ST- elevation myocardial infarction

Myocardial infarction is almost always because of the formation of a thrombus at the site of erosion or rupture of an atheromatous plaque in a coronary artery. If the thrombus formed completely occludes the vascular lumen, ST elevation myocardial infarction is the result.

The process of infarction progresses over a period of several hours and therefore most of the patients present when it is still possible to salvage myocardium and improve the outcome.

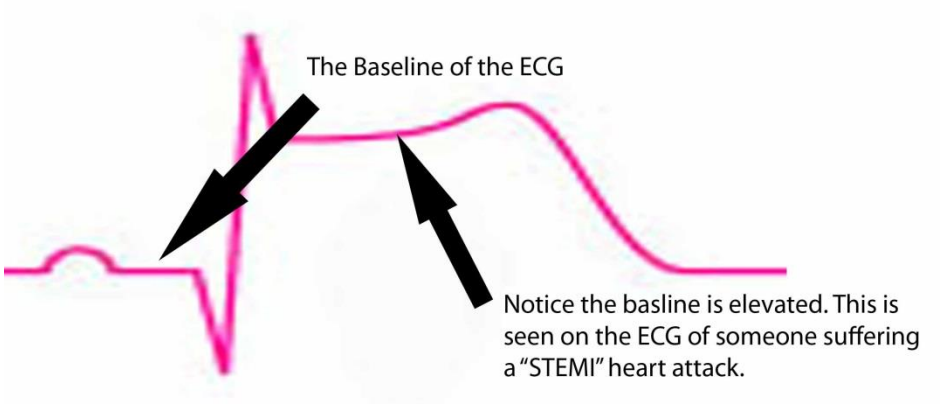
Clinical features

Pain is the cardinal symptom of myocardial infarction. Pain occurs at the same site as that of angina pectoris but it persists even during rest, is more severe and is more severe and lasts longer. The pain is described as tightness, heaviness or constriction in the chest. (6).

There may be symptoms of sympathetic over activity associated with the pain. Breathlessness may be present along with the pain but sometimes it may be the only symptom. Pain may also be absent in diabetic patients or old patients.

Syncope or even sudden death from ventricular fibrillation or arrhythmias may occur immediately. Most of the deaths occur during the first 24 hours. Of these deaths majority of them occur in the first hour.

Diagnosis



The electrocardiogram is the cornerstone of diagnosing STEMI (2).

There is ST segment elevation in two or more contiguous leads, during the early hours of the disease. Soon it is followed by loss of the R wave over some hours. T wave inversion occurs within a few days and over some days to weeks, a well-established Q wave is formed.

Patients with typical symptoms of Acute myocardial infarction with the characteristic findings on ECG are diagnosed as ST- elevation MI and are candidates for fibrinolysis, after considering the time duration after the onset of symptoms, with the absence of contraindications.(7)

Biomarkers

The biomarkers most employed for diagnosis are Creatine Kinase – cardiospecific isoform (CK-MB), and other cardiospecific proteins Troponin-T and troponin-I. CK-MB starts to rise at six hours, peaks at 12 hours and falls to normal within three days. The cardiac troponins are elevated after 6 hours and remain elevated up to two weeks.(6).They are most important in the diagnosis of Non ST elevation Myocardial infarction. They are also important in assessing the progression of STEMI also.

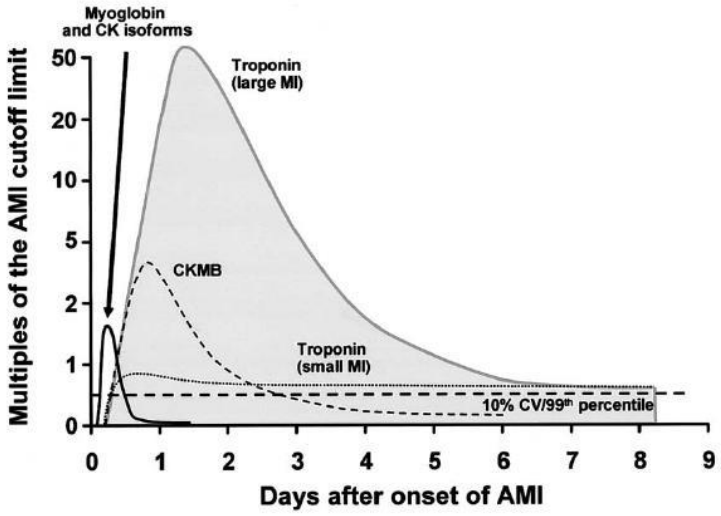


Figure 3. Time course of the appearance of various markers in the blood after acute myocardial infarction (AMI). Shown are the time concentrations/activity curves for myoglobin and creatine kinase (CK) isoforms, troponin after large and small infarctions, and CK-MB. Note that with cardiac troponin some patients have a second peak in addition. CV = coefficient of variation.

Chest X ray may reveal pulmonary oedema not detectable by clinical examination. Echocardiogram may detect cardiac rupture, mitral regurgitation, ventricular septal rupture, pericardial effusion, mural thrombus.

Management

Immediate measures:

The patient must be shifted to a coronary care unit with defibrillation facilities. I.V access is obtained immediately. Aspirin 300 mg is given immediately, along with 40-80 mg of atorvastatin. Intravenous analgesia using opiates is of very high importance.

Reperfusion therapy:

Reperfusion can be attempted using either fibrinolytic therapy or primary percutaneous intervention- primary PCI.

Fibrinolysis: This is cheaper and more readily available than percutaneous intervention. Maximum effectiveness is achieved if it is performed within one hour. Benefit is still high if it is performed within 6 hours. Some benefit still remains if it is done within 12 hours. The risks outweigh the benefits after 12 hours have passed.

Primary PCI: When compared to fibrinolytic therapy, it is associated with a fifty percent greater reduction in risk of death and recurrence of myocardial infarction. (6). However it is not widely available. It may be attempted if fibrinolytic therapy has failed, especially in the setting of pump failure leading to pulmonary edema and/ or cardiogenic shock.

Maintaining Patency of Vessel wall: Anti-platelet therapy: Daily oral administration of aspirin(75-300 mg) improves survival(1). There is a thirty per cent reduction in mortality. Clopidogrel 75 mg may be added as an antiplatelet as it further increases survival rates.

Statins: Atorvastatin 20-40 mg daily not only acts as a lipid lowering drug, but also has a pleomorphic effect whereby it reduces the pro-inflammatory state and improves survival.

Anticoagulants: Heparin when administered in addition to antiplatelets prevents reinfarction after fibrinolysis. It also reduces the risk of thromboembolic complications.

Adjunctive Therapy:

Nitrates: They are useful in relieving pain and for treatment of Left ventricular failure.

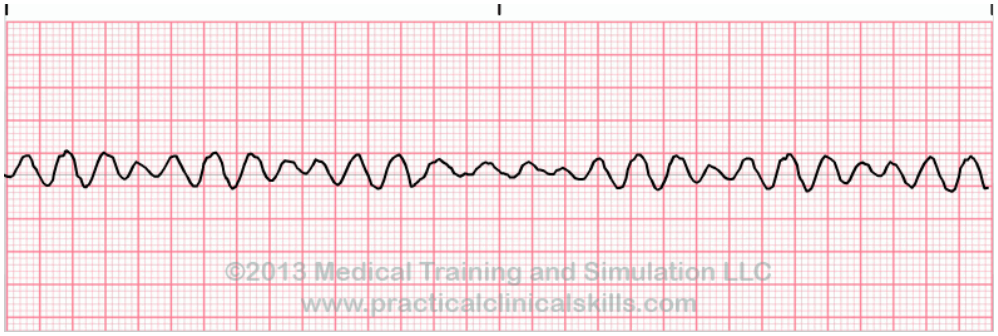
Beta blockers: Intravenous beta blockers are useful in reducing pain and in preventing arrhythmias, during the first 12 hours. They also improve short term mortality.(8)

ACE inhibitors: They are useful in their action against left ventricular remodelling that may occur in the aftermath of an acute myocardial infarction.

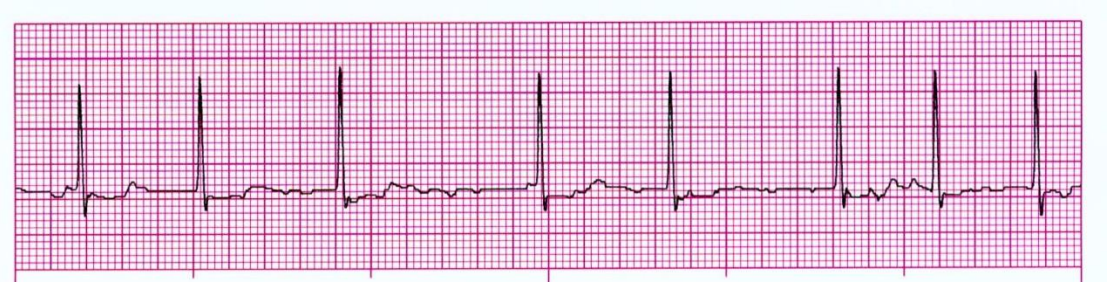
Complications:

Arrhythmias:

Ventricular fibrillation: This occurs in 5-10% of those who reach the hospital. Quick defibrillation will usually restore sinus rhythm.

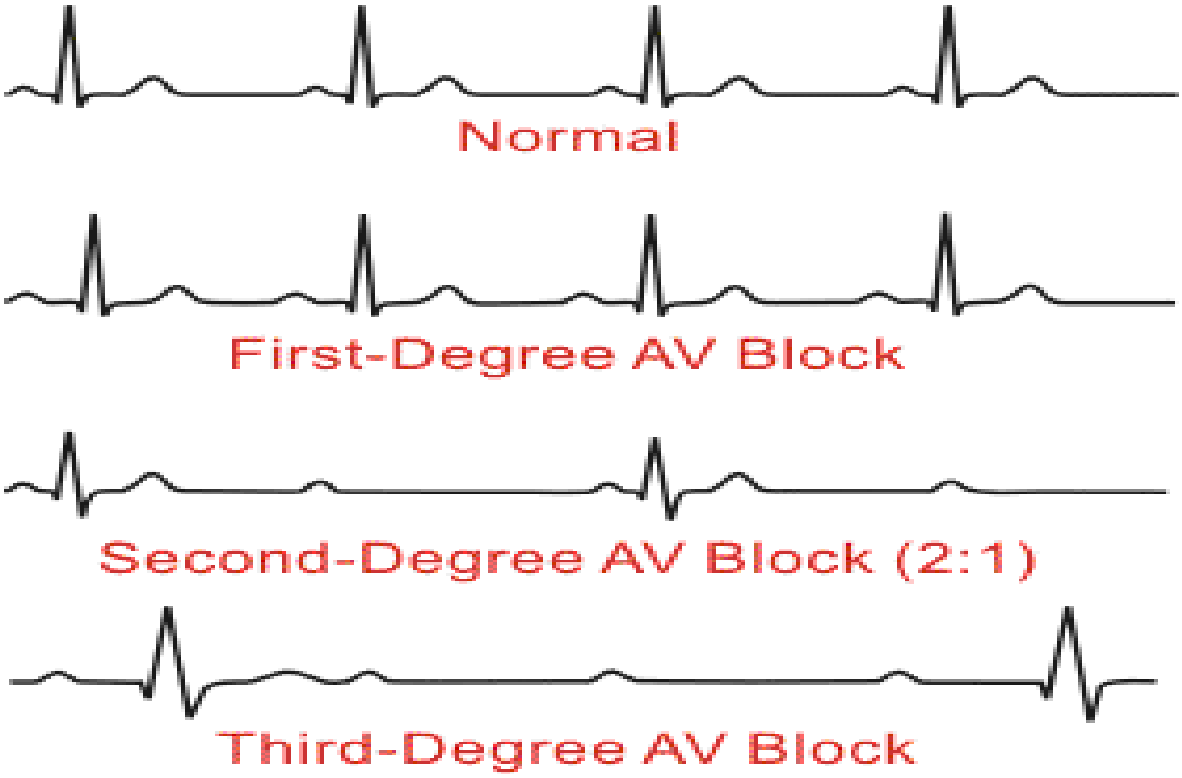


Atrial fibrillation: This is transient and may not require treatment. However if it is sever enough to cause circulatory collapse, cardioversion by synchronised DC shock must be given.



Sinus Bradycardia: Does not require treatment. Except in cases of hypotension where atropine may be administered.

Atrioventricular Block: Usually temporary. May respond to atropine. If there is hypotension or second/third degree block, a temporary pacemaker should be considered. (8)



Ischemia:

Post infarct angina occurs in upto 50% of patients. They should be managed similar to patients with unstable angina.

Acute Circulatory failure:

This reflects extensive myocardial damage. This usually indicates a poor prognosis.

Pericarditis: Most common on the second and third day. NSAIDs and steroids are to be avoided as they increase the risk of wall rupture. Opioids are preferred. *Dressler's syndrome* (fever, pericarditis) occur after a few weeks of the infarct. It Can be treated with NSAIDs.

Papillary muscle damage: May cause acute MR and pulmonary edema. Surgical intervention may be needed in severe cases.(7)

IV septum rupture: It is a rare complication. Without prompt surgery, the condition is usually fatal.

Rupture of ventricle with cardiac tamponade: Usually fatal. Mild cases can be saved by early surgery.

Ventricular remodelling: The infarct thins out and becomes inefficient in pumping. The left ventricle enlarges over a few months to years. This is called

remodelling. This progressively reduces the cardiac function. ACE inhibitor therapy reduces this phenomenon.

Ventricular aneurism: It occurs in ten per cent of patients. It may lead to heart failure, ventricular arrhythmias, mural thrombus and systemic embolism. It causes a persistent ST elevation in the ECG. Surgery for removing the aneurism carries a very high mortality. So it must be undertaken only when absolutely necessary.

Reperfusion injury

Even though reperfusion of the critically ischemic myocardial tissue is beneficial as it salvages the still viable myocardium, this may come at a cost of a process called as reperfusion injury. (9) There are many types of reperfusion injury.

1. Lethal reperfusion injury: This is the reperfusion induced death of cells that were still viable at the time of restoration of coronary flow.
2. Vascular reperfusion injury: this is the progressive damage to the microvasculature. There is an expanding area of no reflow and loss of coronary vasodilatory property.
3. Stunned myocardium: Salvaged myocardium may display a prolonged period of contractile dysfunction, even after restoration of blood flow.

4. Reperfusion arrhythmias: there may be bursts of ventricular tachycardia and occasionally, ventricular fibrillation.

Reperfusion increases the cell swelling that occurs with ischemia. There may be a creation of a haemorrhagic infarct.

Fibrinolytic therapy appears more likely to produce haemorrhage into the infarct than catheter based reperfusion. However the haemorrhage does not extend beyond the area of myocardial necrosis. So there is no infarct extension.

Reperfusion arrhythmias: There may be a transient sinus bradycardia in patients with inferior wall infarction. This is mostly associated with some amount of hypotension. (10)

Other common reperfusion arrhythmias are premature ventricular contractions, accelerated idioventricular rhythm, and non-sustained ventricular tachycardia.

When reperfusion arrhythmias are present, they may actually indicate a successful restoration of coronary flow. Reperfusion arrhythmias have a high sensitivity for detecting successful reperfusion. This is especially important, considering the fact that clinical features are poor markers of myocardial reperfusion.

The arrhythmias show a temporal clustering during the time of restoration of coronary blood flow with successful fibrinolytic therapy, the overall incidence of such arrhythmias seems to be similar in patients who do not receive fibrinolytic agent. The brief electrical instability that occurs during reperfusion is generally innocuous and can be thought of as not life threatening. Considering the above factors, one may conclude that no prophylactic antiarrhythmic therapy is essential when fibrinolytics are prescribed.

Magnesium in the human body

Tissue Distribution

The Entire human body consists of 760 milligrams of magnesium during birth. When one reaches five months of age, it will contain 5 grams of magnesium. When adulthood is attained, the entire body would contain up to 25 grams of magnesium.

When we consider about the distribution of magnesium inside the body, we find that, thirty to forty per cent is confined inside the human musculature, the entire soft tissue mass, one per cent is found inside the extracellular fluid compartment of the body. The remaining fifty to sixty per cent is found inside the

skeletal system, where it is chemically combined with calcium salts in the form of hydroxy-apetite. Magnesium is calculated to be one per cent by weight of bone ash.(11,12)

Functions

The magnesium that is present inside the soft tissues has many important functions. It is a co-factor for many enzymes and proteins involved in metabolism of nutrients to release energy. It is also needed in enzymes for synthesis of proteins, synthesis of DNA, creation of RNA. It is indispensable, for maintaining the electrical potential across a cell, which is responsible for the creation of resting membrane potential, especially in cells like the neuron, the myocytes, and smooth muscles and such.

Between fifty and sixty per cent of magnesium inside the human body is inside the skeletal system. It forms an important constituent of hydroxyl apetite(calcium phosphate), which is a mineral component. The important point is that, initially a significant amount of this magnesium can easily be exchanged with the serum. Thus bone stores are a relatively easy access site for serum magnesium, during times of deficiency. As the age advances, this process becomes less and less efficient. So the exchangeable fraction declines very significantly with increasing age(13).

Magnesium levels influence the potassium influx and efflux across the body compartments. It is also involved in the metabolism of calcium ions.(14,15). The depletion of magnesium reduces significantly, both intracellular and extracellular levels of potassium. It magnifies the effects of a low potassium diet. The reduction in muscle potassium levels is marked as magnesium deficiency develops. The replenishment of potassium is near to impossible unless the magnesium levels are restored to normal.

There is development of low calcium levels in the plasma as the magnesium levels begin to drop. The exact reason for this phenomenon is unclear. Possible explanations include the inhibition of parathyroid hormone, secretion, directly or indirectly. A more probable explanation would be the reduction of the bone sensitivity to the action of parathyroid hormone. So in effect, there is reduction or restriction of removing calcium from the bone stores towards the serum.

One important finding is that, when the diets of patients who suffered from gluten sensitive enteropathy were fortified with magnesium, many physiological events took place. There was significant increase in the bone mineral density of the femur. There was also increase in the levels of intracellular magnesium inside the erythrocytes.(16)

Dietary sources

Deficiency of magnesium in the normal diet is usually not very severe. So, dietary deficiency itself does not usually cause pathological changes of significant severity. Magnesium is distributed broadly in foods of plant and animal sources. Geological, chemical, and environmental variables are usually of little importance so as to have a major influence on the magnesium content inside common foods.

Most legume seeds, green leafy vegetables, peas, nuts, and beans are rich in their magnesium content. Other sources include Shellfish, soya flour, many spices, molluscs and seafood. They usually contain more than 500mg/kilogram magnesium content. Even though, most of cereal grains that are unrefined, are sources with a reasonable magnesium content, many fully refined flours, tubers, roots are poor in magnesium content. Magnesium content is also very low in Fruits, fungi, most of the oils and fats. The foods that have very low magnesium content are Corn flour, cassava or tapioca, polished rice flour, sago flour, etc.

Around fifty to ninety per cent of magnesium from mothers milk is absorbed by the infant. This can be considered as a very effective absorption mechanism. When studies on adult population were conducted, the results varied considerably. There seems to be a homeostatic capacity of the body to adapt according to the wide variations of intake of dietary magnesium. (17, 18).

The site of absorption of magnesium appears to be greatest within the duodenum. Illeum also is a major site if absorption. (19). The absorption seems to have two mechanisms. One is an active process and other is a passive process.

When the dietary fibre intake increases, there is a reduction in the amount of magnesium that is absorbed by the intestines. (20,21). There is a magnesium binding compound in the dietary fibre. These are the phytates. The paradox is that, the food that is rich in phytates is also rich in their magnesium content. So there is no reduction in body magnesium levels on consuming a high fiber/phytate diet.

Excretion

The kidneys have a very important role in the homeostasis of magnesium inside the human body. There is active reabsorption of magnesium that takes place in the loop of henle. It also occurs in the proximal convoluted tubule. The excretion and reabsorption of the ion is very much influenced by the concentration of sodium in the urine, It is also influenced by the acid base balance.(23).

Dietary changes that caused a change in the acid base balance of the urine in the favour of alkalosis, resulted in a reduced excretion of magnesium through the urine. To be more precise, the urinary magnesium levels dropped by up to thirty five per cent.(22).

Several other studies show that dietary intake of calcium more than 2600mg/day, along with a high sodium chloride intake, is responsible for a shift towards negative magnesium balance, by increasing its excretion through urine.

Other routes of excretion of magnesium are via the gastrointestinal tract. This is mainly via the magnesium content inside the epithelial cells of the intestine that is lost as a normal repair and regeneration process. This is not a significant route. Other non-significant route of excretion is via the sweat, during vomiting, diarrhoea and other fluid losses. Since much of the magnesium is intracellular, these losses do not significantly affect total body magnesium.

Estimated Allowances of magnesium

Age Group	Magnesium requirement(mg/day)
0-6 months	26
7-12 months	54
1-3 years	60
4-6 years	76
7-9 years	100
Adolescents (10-18years)	

Males	230
Females	220
Adults(19-65 years)	
Males	260
Females	220
65+ years	
Males	224
Females	190

One important point to consider is that, there is no increase in dietary magnesium needed in case of pregnancy. However, there is a need to increase the levels of magnesium consumption during the periods of lactation. The required increase is 50mg/day.

Upper tolerable limit

Reaching the upper tolerable limit through diet alone is very much unlikely. No case has been reported so far. However there is the possibility of contamination of food and water sources with elementary magnesium, most commonly with magnesium salts. (24)

Age group	Upper limit of magnesium consumption
Children(1-3 years)	65mg
Children(4-10 years)	110 mg
Adolescents	350 mg
Adults	350 mg

Signs and symptoms of hypomagnesaemia are mostly nonspecific. The most common ones are nausea, diarrhoea and hypotension. The hypotension may be a direct effect of magnesium and not always due to dehydration because of diarrhoea and/or vomiting.

Origins of Magnesium deficiency

Nutritional deficiency that leads to pathological processes and eventually to symptoms is infrequent in infants. They are even rarer in adults.

It is however possible in very rare circumstances. One example of such an event would be relatively low magnesium content in diet along with prolonged diarrhoea that is severe. Or when dietary deficiency of magnesium is coupled with urinary

loss of magnesium, especially if the diet results in reduction in pH levels of urine or a relatively acidic urine.

Other scenarios include the conditions in which there is increased demand for magnesium, and the body is unable to provide the necessary nutrient. For example, when an individual is getting rehabilitated from general malnutrition with macronutrients alone, without the necessary micronutrients, there is increased susceptibility to the effects of magnesium deficiency.(16)

Many studies have been conducted that show that there is a decline in the excretion of magnesium via the urine, during protein energy malnutrition (PEM)

It is also accompanied by a reduced absorption of magnesium through the intestines. When one is recovering from protein energy malnutrition sates like kwashiorkor and marasmus, we can expect a period of catch-up growth. This is not achieved if the dietary magnesium levels are not increased substantially (16).

Effects of magnesium deficiency

The early pathological processes and consequences caused by magnesium depletion mostly affect the nervous system. It also effects neuromuscular system. The reason behind this is not unclear. It may be because of the influence of magnesium on the efflux and influx of potassium between tissues and between the intracellular and extracellular compartments.

Decline in the status of magnesium in the body causes anorexia associated with nausea as the most common symptom. Other symptoms are lethargy along with muscular weakness. Staggering is also seen. If the duration of magnesium deficiency is prolonged, it may result in significant weight loss.

As the magnesium levels progressively decrease, gradually other symptoms appear. These symptoms are generally more bothersome. The primary process or pathology in magnesium depletion is hyper irritability or hyper excitability of neurons, neuromuscular junctions and the connections between the muscles. It means that these cells get exited from their resting membrane potential to give rise to an action potential more easily than before. In other words, the threshold for excitation is reduced and also the magnitude of the exiting current is also reduced.

This leads to muscular spasms and tetany. The severity of these symptoms is highly variable. They may be mild and transient to highly disabling. They may ultimately lead to convulsions. It is a common medical practice to infuse magnesium in cases of eclampsia. This shows the importance of magnesium in preventing and also in arresting convulsions.

In experimental animals a peculiar observation was made. The animals that had a lower magnesium levels in their body were more susceptible to audiogenic shock.

Fatal consequences are also seen. These include cardiac arrhythmias and pulmonary edema. Cardiovascular mortality is the number one cause of deaths in the world. Magnesium levels thus seem to play an important role in such an important health condition.

Certain studies have suggested that a sub-optimal magnesium status, not necessarily a established hypomagnesaemia, may be a risk factor in the etiology of coronary artery disease. It may also be a risk factor for systemic hypertension.

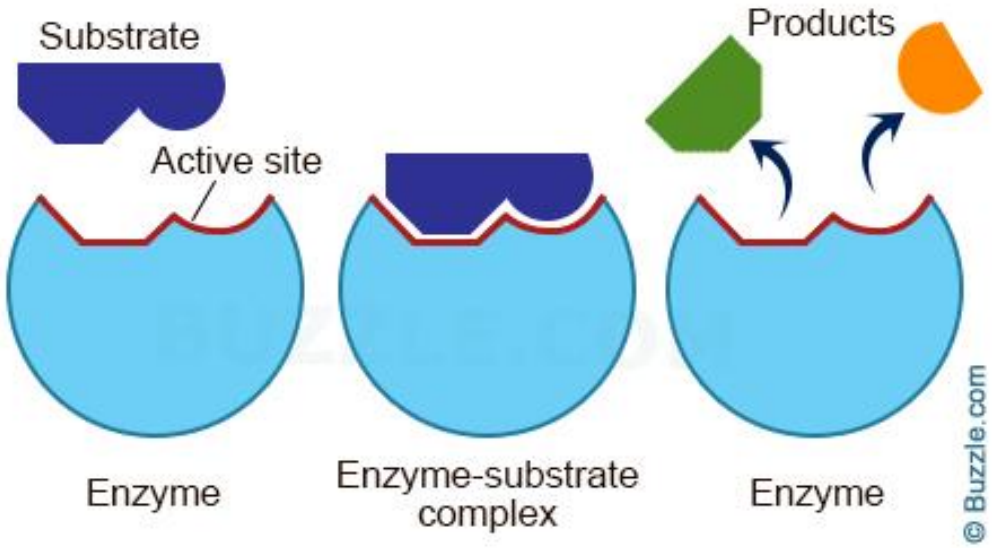
If they are indeed true, more insight and research is needed into the relationship between magnesium and the heart. The fact however remains that additional evidence is needed to establish a definite link between magnesium levels in the body and cardiovascular disease.

ENZYMES and MAGNESIUM

ENZYMES

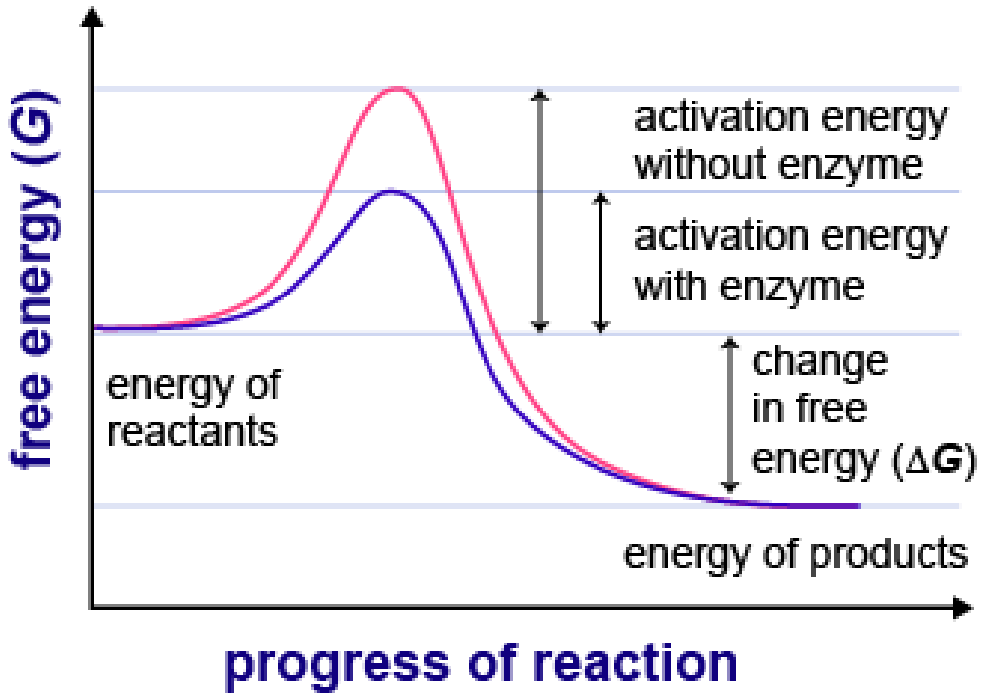
Enzymes are complex proteins that are responsible for the catalytic action of certain chemical reactions. Generally speaking these are biochemical reactions. Most of these biochemical reactions take place inside the body or in-vivo. But as in all cases there are exceptions. Bacteria produce enzymes to ferment sugars to produce alcohol and carbon di oxide. In fact this was one of the first enzymatic

biochemical reactions discovered which paved the way for future research into the functions and properties of enzymes.



The above diagram illustrates how an enzyme functions. The enzymes bind temporarily with the chemical molecules that are taking place in the biochemical reactions. For both of the chemical substances to react with each other, both of them much reach a specific energy level called activation energy. What the enzyme effectively does is that it reduces the activation energy needed for the desired chemical reaction to take place, so the speed of the reaction that occurs in the desired direction increase many folds.

The following graphical representation illustrates how the enzyme reduces the activation energy that is required for the initiation of a chemical reaction and thus speeds up the reaction in one specific direction.

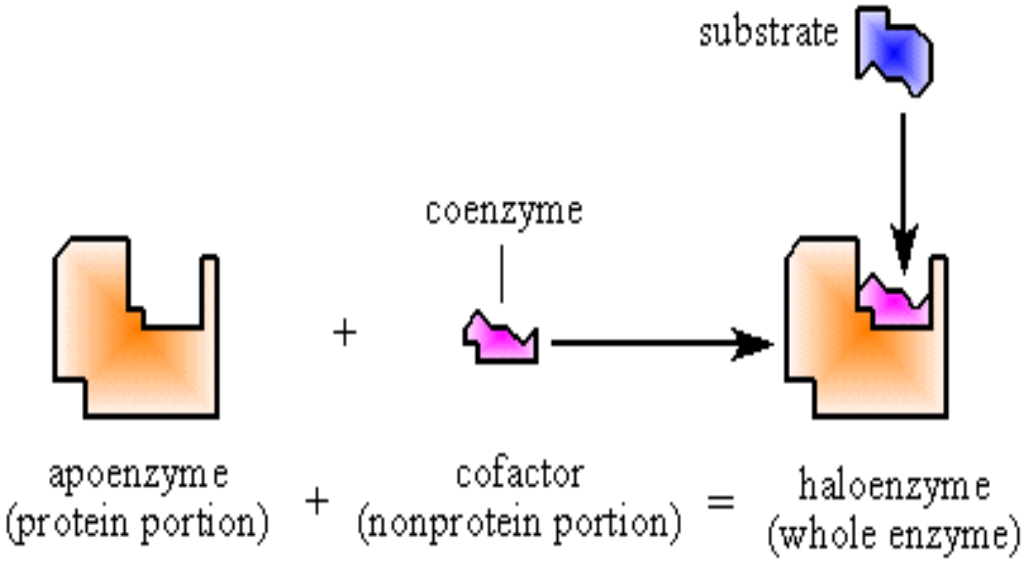


Coenzymes and cofactors

Cofactors can be considered as a part of an enzyme. In other words, enzymes are not always a single molecule. Sometimes it may be formed of multiple sub-units or parts. The entire enzyme functions optimally or normally only when the cofactor part is attached to the other part of the enzyme.

Here the incomplete enzyme without the cofactor can called as an apoenzyme. When the apo- enzyme and the co-factor join together we get the completely functioning enzymes called as holoenzymes.

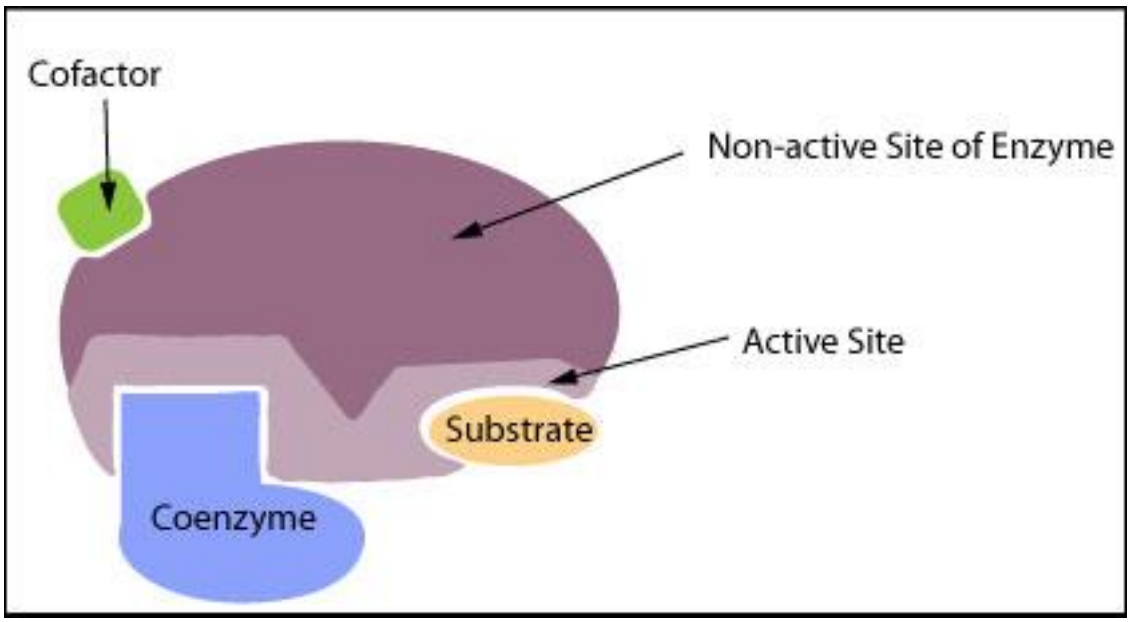
One important thing to keep in mind is that the co-factor is not a protein, unlike the apoenzyme which is a protein.



Coenzymes are different from co-factors. Co-enzymes often act as carriers of electrons or carriers of hydrogen ions from one substrate to the other in an enzymatic reaction.

Coenzymes bind to the active site of the enzymes which is involved physically in the manipulation and binding of the substrates. Co-factor are the non-

protein part of the enzyme, which is mostly bound to the inactive site of the enzyme, not involved in the binding and release of the substrates that are involved in the biochemical reaction.



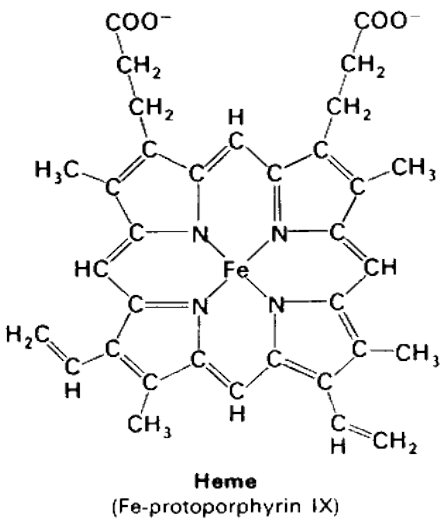
Prosthetic groups are coenzymes that are bound to an apoenzyme very tightly. N most cases there is a covalent bond between the prosthetic group and the remaining part of the enzyme.

Cofactors can be divided into two types.

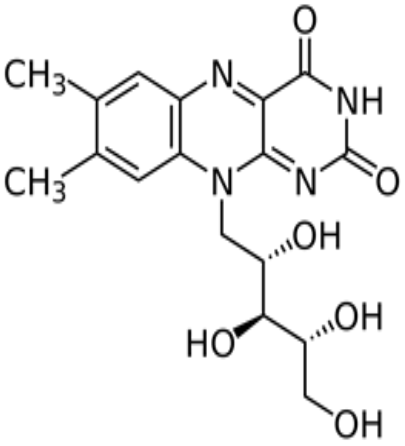
1. Organic Cofactors

2. Inorganic Cofactors

Organic cofactors include molecules like heme, flavins



HEME



FLAVIN

Inorganic Cofactors like metallic ions.

1. Magnesium (Mg 2+)
2. Zinc (Zn2+)
3. Manganese (Mn2+)
4. Iron (Fe2+)
5. Iron sulphur clusters.

Enzymes requiring magnesium as a cofactor

If you count the total number of enzymes that require magnesium as a cofactor in the body, in comes to around three hundred. A complete enumeration of these enzymes are beyond the scope of this discussion.

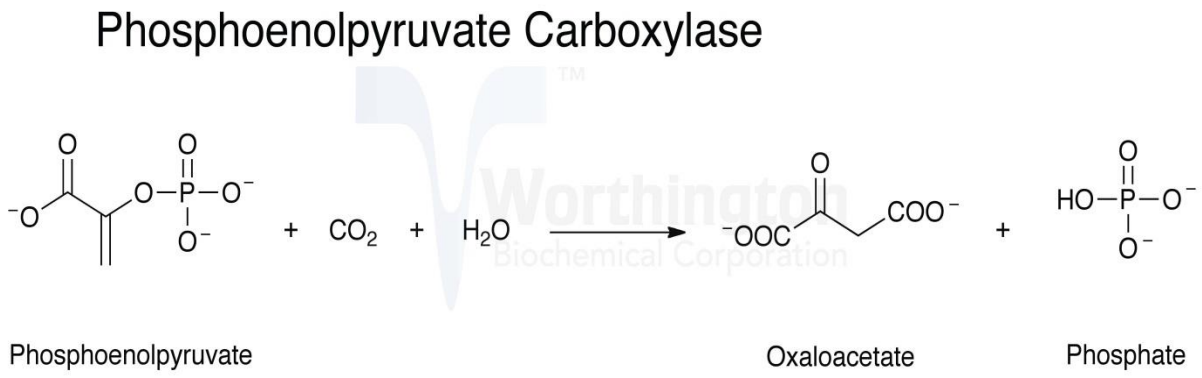
However we shall brifly describe the most important group of enzymes and their functions in the human body

The Carboxylases

Carboxylation: Carboxylation as a biochemical reaction in which a carboxyl group is attached to a substrate. The opposite process id called as decarboxylation.

Examples include:

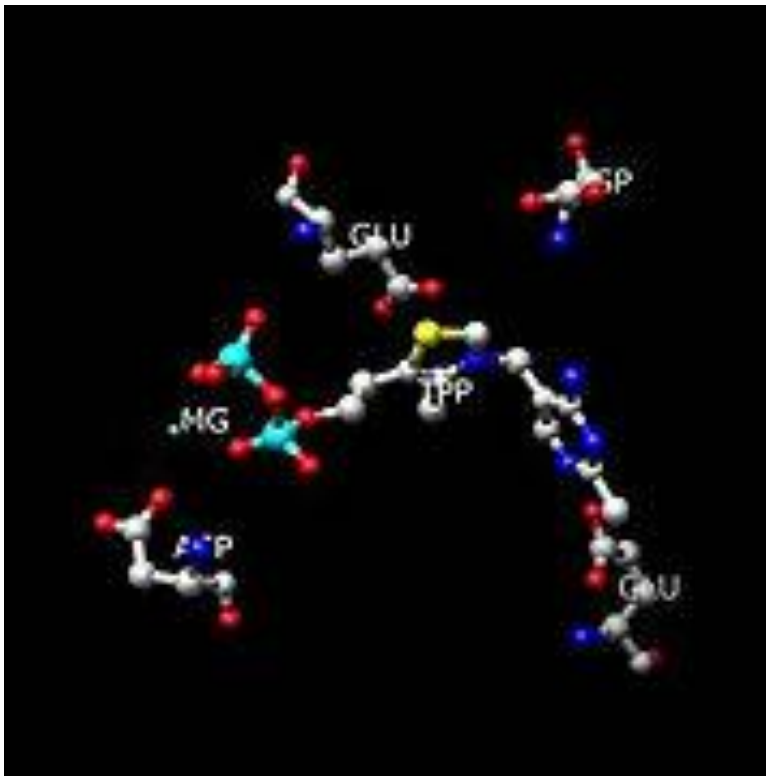
1. Pyruvate carboxylase enzyme
2. Acetyl CoA carboxylase
3. Phosphoenol pyruvate carboxylase.
4. Propionyl CoA carboxylase.



The carboxylases allow the addition of new carbon molecules into the substrate from CO2 molecule or HCO3- molecule. They are divided into teo types based on cofactor requirement. One type requires biotin and others require vitamin K.

One of the important functions of carboxylases in the body is the synthesis of biomolecules.

Carboxylases are involved in fatty acid synthesis, carbohydrate synthesis and many other reactions.



Pyruvate carboxylase.

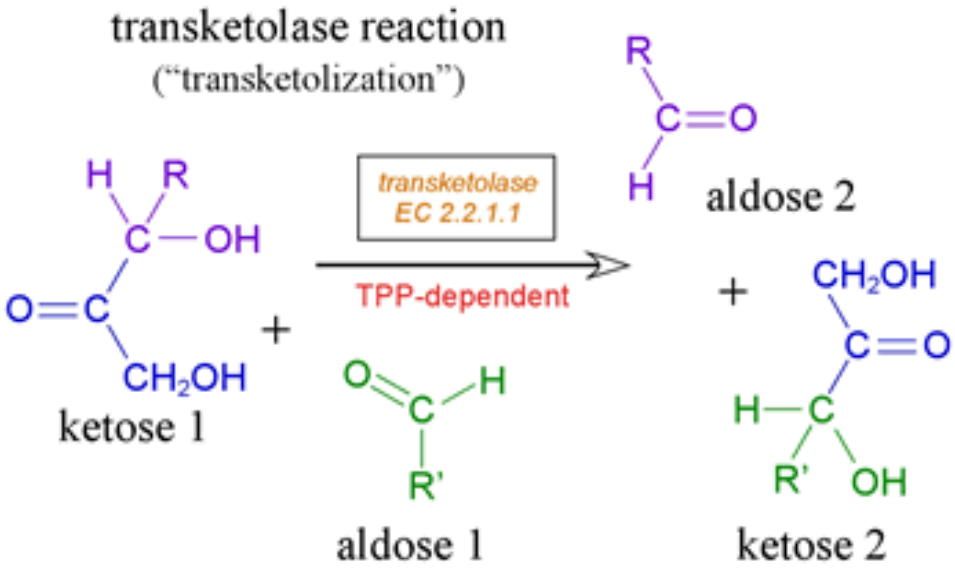
As shown in the above figure magnesium ions are an important prosthetic group or cofactor in the entire carboxylase group of enzymes. This magnesium plays an important role in fatty acid production carbohydrate metabolism and other important reactions.

Transketolases

Transketolases are enzymes that play a very important role in the pentose phosphate pathway that is present in virtually all organisms including humans. Interestingly it is also present in the calvin cycle of photosynthesis.

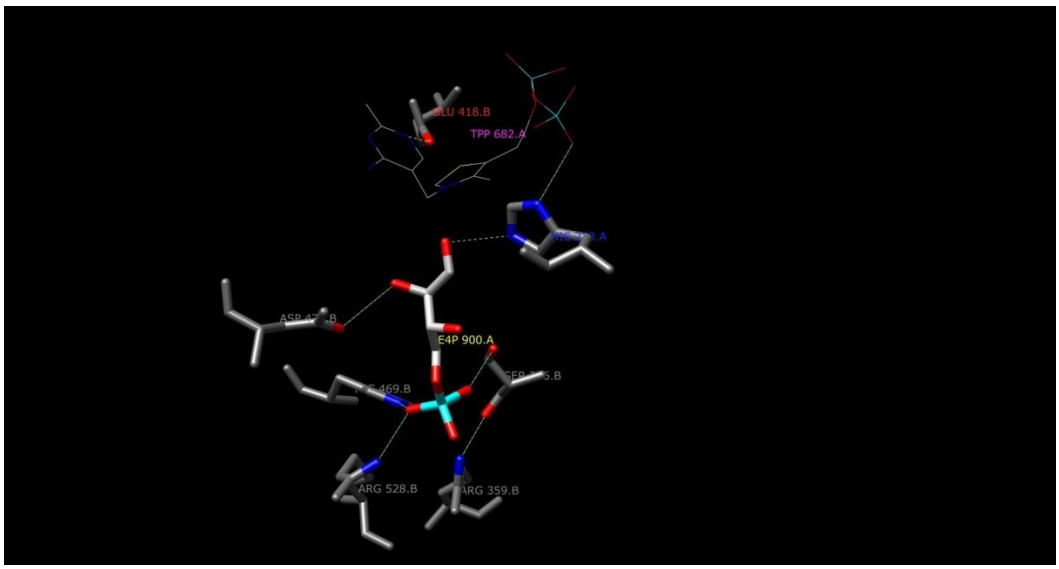
It catalyses two important reactions.

1. The cofactor of the enzyme, TPP ot thiamine pyrphosphte transfers a two carbon segment from a five carbon xylulose to a five carbon ribose to form a seven carbon molecule called as sedoheptulose.
2. The second reaction involves the transfer of the two carbon fragment from Xylulose to the four carbon atom containing erythrose, resulting in the formation of the six carbon Fructose 6 phosphate and glyceraldehyde 3 phosphate.



Transketolases are thus responsible for the bio synthesis of NADPH which in turn is responsible for many of other synthetic reactions of the human body.

NADPH is also responsible for the replenishment of glutathione which is one of the most important anti-oxidant molecules of the human body.



Transketolase is the connecting link between the pentose pathway and glycolysis. The excess of sugar phosphates is thus shunted into the carbohydratr pathway.

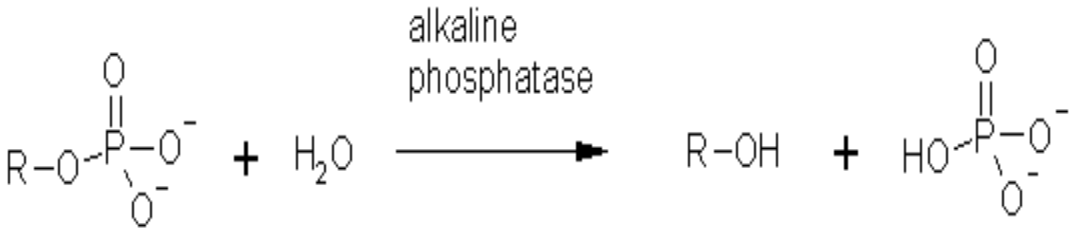
Magnesium is an important prosthetic group of the transketolase enzymes and is thus indirectly responsible for the anti-oxidant abilities and carbohydrate metabolism of the body.

Phosphatases

Phosphatases are enzymes that are capable of removing a phosphate group from a substrate.

They achieve this by hydrolysing phosphoric acid. After hydroxylation, we get a phosphate ion and a molecule with a free hydroxyl group.

The action of phosphatases is exactly opposite to the action of kinases and phosphorylase, in which a phosphate molecule is added to a substrate from high energy molecules like ATP.



Importance of phosphatases in human physiology

The action of a phosphatase is opposite to that of kinases or phosphorylases, which in turn add a phosphate group to a protein or enzyme. The process of addition of an enzyme may result in activation of the enzyme or deactivation of the enzyme. It may also result in a protein to protein interaction.

Phosphatases are thus important in many of the signal transduction pathways.

Phosphorylation of proteins plays an important role in many biological functions. These include:

1. Metabolism,
2. Gene transcription,
3. Gene translation,
4. Cell-cycle progression,
5. Cytoskeletal rearrangements
6. Protein protein interactions
7. Cell movement
8. Apoptosis.

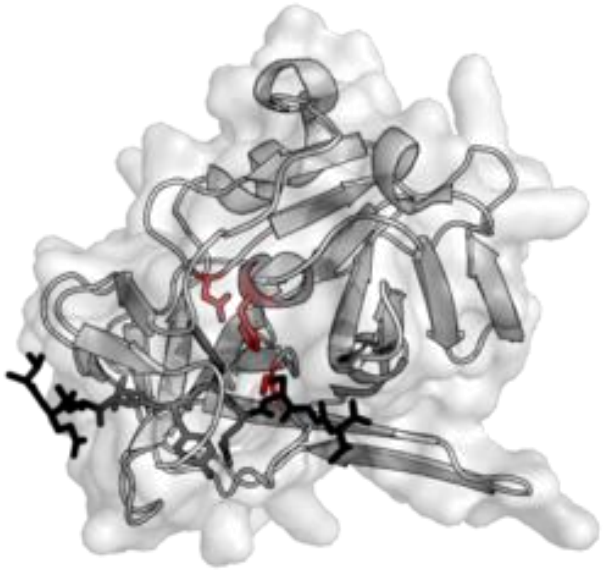
Magnesium is an essential component of the phosphorylase group of enzymes. So magnesium is essential in all the biological processes enumerated above.

Memory and learning

In the adult brain, protein phosphorylation is involved in many neuro biological processes. Dysfunction of the enzyme has been linked to various neurodegenerative processes and cognitive degeneration.

Peptidases

Peptidases are also known as proteases. They are responsible for the cleavage if protein molecules or peptide molecules.

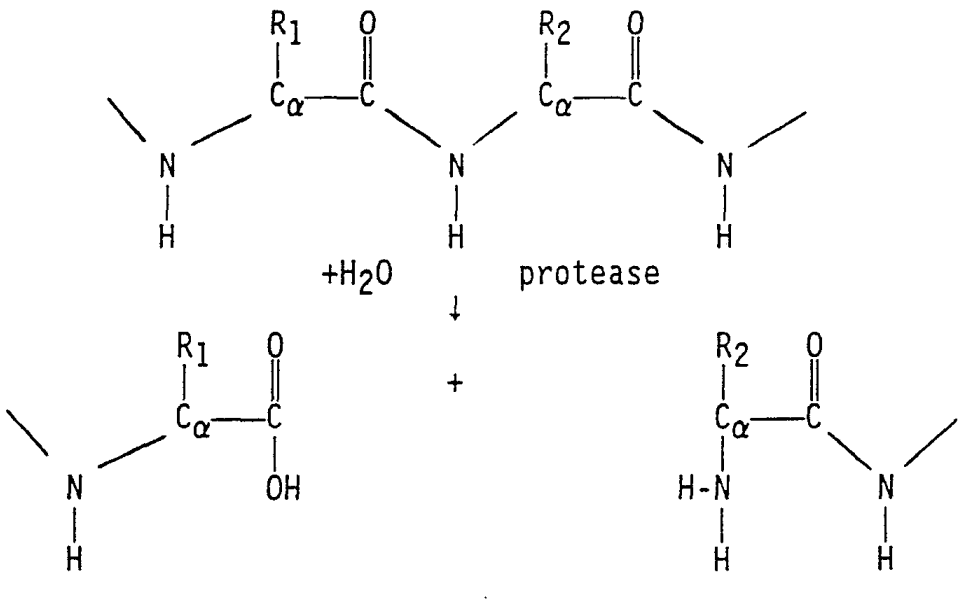


Examples of proteases in the human body.

1. Digestive system. Pepsin, trypsin, are some of the proteases that are present in the digestive juices of the human body . These are invaluable in the proper digestion, and nutrition of the human body.

2. Haemostasis: Many of the protease enzymes are present in the serum of human body. They are activated in the event of haemostasis and also in lysis of the clot that is formed. Some of the examples of such protease enzymes in the serum are, thrombin and Hageman factor. These are involved in blood clotting. Plasmin is also a protease enzyme. It is involved in clot lysis .

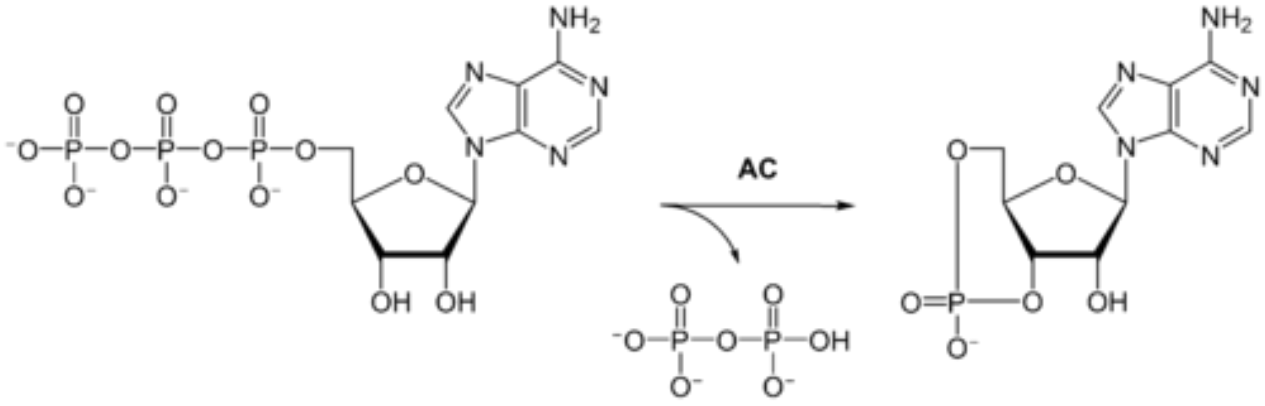
3. Leucocytes: Many proteolyic enzymes are present in the leucocytes. Leucocytes are responsible for the immune mechanism of the body. Some of the protease enzymes that are present in leucocytes are, elastase and cathepsin G. Elastase functions as the enzyme that acts on the elastin protein.



Magnesium is a prosthetic group of the protease group of enzymes, without which, these enzymes will not function properly. So magnesium ions are also essential for the above mentioned life processes.

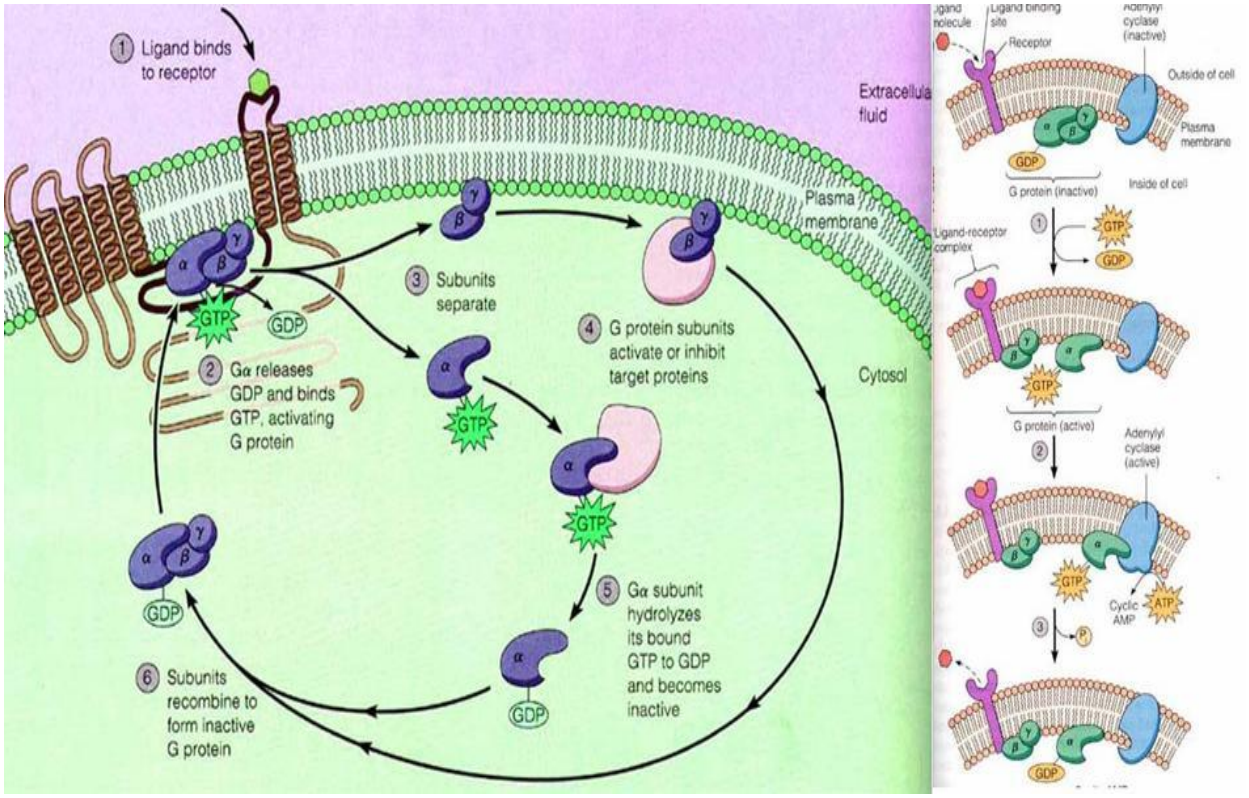
Adenylyl cyclase

These are a class of enzymes. All classes of these enzymes are involved in catalysing the conversion of ATP (Adenosine Tri Phosphate) to cAMP or cyclic Adenosine Mono Phosphate.



The cyclic AMP thus produced have a special role. They act as a secondary messenger or as a regulatory signal by binding to certain cAMP binding proteins. These proteins may be enzymes or transcription factors.

For example in the sympathetic system, adrenaline binds to the beta receptors located on the cell membrane. The beta receptor is a G protein coupled receptor. As the receptor binds to the ligand, the enzyme adenylyl cyclase is activated, resulting in the production of cAMP or cyclic amp molecules which bind to certain cAMP binding proteins intracellularly and thus propagates the cascade of intra-cellular changes.



The adynelate cyclase enzymes are usually coupled to G-Protien receptors. The G protein couple extracellular receptors are essential for all the cells are they enable those cells to communicate signals between other cells and also the external environment.

The messengers reaching the extracellular receptors need to transfer the message to the intracellular organelles. His is accomplished by the adenylate cyclase enzyme and the cyclic AMP based secondary messenger system.

Magnesium is an important cofactor of the adenylate cyclase enzyme.

Ribonuclease

Nucleases are enzymes that catalyse the degradation of nucleic acids into smaller components. There are mainly two types of nucleic acids. DNA(De- oxy Ribonucleic acid) and RNA(Ribonucleic acid).

Ribonucleases are enzymes that are involved in the degradation of RNA or ribonucleic acid into smaller components.

There are two types of ribonucleases.

1. Exonucleases
2. Endonucleases

Structure of RNAase A

Functions:

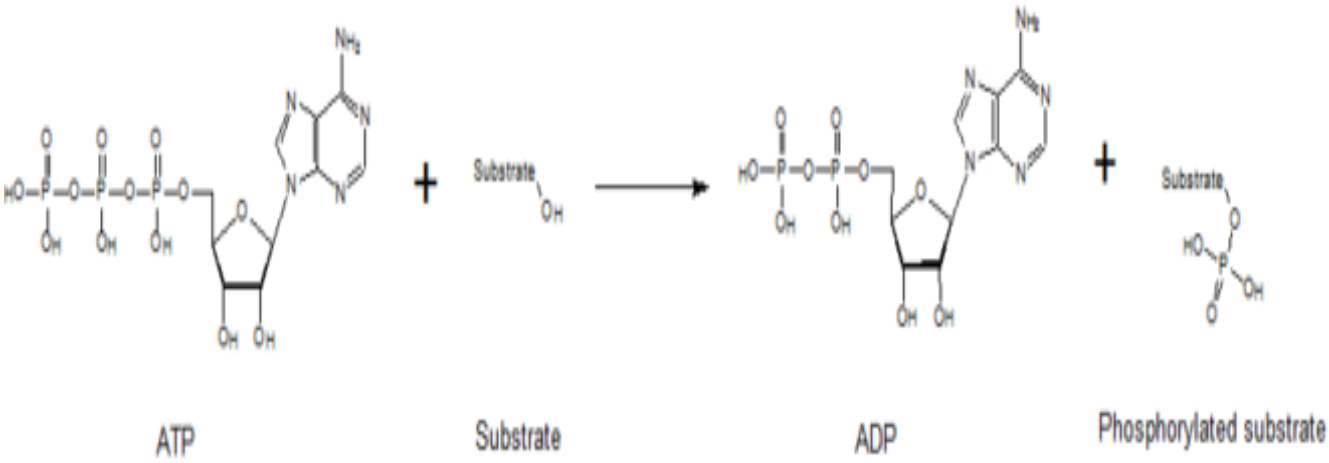
All of the living things studied contain many RNAses of many different types., showing that the process of RNA degradation is evolutionary very ancient and important. Apart from cleaning of cellular RNA that is not required an longer. RNases play important roles in the complete development and maturation of of all RNA molecules, both messenger RNAs that carry genetic information for creating proteins, and also non-coding RNAs that that have different cellular functions. Apart from this, RNA degrading enzymes are a first line of defence against RNA viruses that may invade the cell and take over the cellular machinery and multiply..

Some animal cells, interestingly secrete large amounts of of non-specific RNases like T1 and A. RNases are, thus, very common. This results in very short lifespans for RNAs. Except for the RNAs that are in a protected and safe environment. One should not that that all intracellular RNAs are protected from the activity of RNA ase by different types of methods. These methods include 5' end capping, 3' polyadenylation. RNA may fold inside a protein RNA comples to escape the ribonucleases.

Magnesium is essential to the functioning of the ribo-nuclease enzyme.

Kinases

Kinase is the enzyme which functions as the one which transfers high energy phosphate molecules from high energy molecules like Adenosine tri phosphate(ADP) to the substrate.



The process performed by kinases is known as phosphorylation.

Kinases should not be confused with phosphorylases. Phosphorlylases add inorganic phosphates to the substrates that are not derived from high energy molecules like Adenosine Tri Phosphate, Guanidine Trti Phosphate etc.

Whether a biological molecule is phosphorylated or not, whether it may be a protein, carbohydrate or lipid may affect its reactivity or its tendency to undergo or ivolve itself in a chemical reaction.

Kinases carry out the transfer of a phosphate ion from a high energy molecule like ATP to another molecule which is the substrate. Kinases are essential to make this reaction stable because the phosphoanhydride bond is a very high energy bond. Kinases cause proper orientation of the substrate and the phosphoryl group. This happens inside their active sites. This in turn increases the reaction speed. In addition to this, they frequently use amino acid residues that are charged positively. This causes electrostatic stabilization of the transition state. by interacting with the phosphate groups that are having a negative charge. In an alternate method, some kinases make use of metallic cofactors which are inside their active sites. They in turn coordinate the phosphoryl groups.

Kinases are utilized widely in transmitting certain signals and also to regulate processes inside cells. Phosphorylation of biological molecules can increase or decrease their activity and regulate their ability in interacting with other bio-molecules. The adding and removing of phosphate groups gives the cell an ability to control. This is due to the fact that different kinases respond to different signals or conditions. Mutations of kinase enzymes that may lead to a loss of function or increase in function can cause malignancy and other illnesses,including some kinds of leukemia, spinocerebellar ataxia (type 14).

Magnesium is the cofactor for the kinase group of enzymes.

Magnesium and the heart

Role of Magnesium in Myocardial Cell Functions

In the myocardium of mammals, the concentration of magnesium is in the sub millimolar range. It varies between 0.3-0.8 millimoles/litre. (27). It is the second most cation, present intracellularly in humans.

A significant amount of magnesium ions are bound to high energy phosphate molecules and also to phospholipids of the cell membrane, inorganic acids, proteins or enzymes. (28).Changes of magnesium concentration intracellularly leads to important effects in the proper functioning of the second messenger systems and ion channels of cardiac cells. Magnesium activates or acts as a catalyst in more than 300 enzymes that are involved in biochemical reactions. It thus functions as a metallocoenzyme. (28, 29)

The Na+/K+ -ATP ase pump requires magnesium for proper functioning.

The Calcium gradient of the cardiac myocyte is maintained partially by the Mg2+ dependent Ca2+- ATP ase system.

There is increasing evidence suggesting that magnesium modulates the cation channels of the sarcolemma, thus exerts a very important and fundamental influence on the electrical function and also the contractile function of the myocardium. (30).

Thus we can see that manifest or hidden magnesium deficiency can make the atrial and ventricular myocardium electrically unstable and increases its tendency to produce dangerous arrhythmias.(31,32).

When there is myocardial ischemia or infarction, the affected myocardial region also losses magnesium in addition to other ions. But newer data suggests that there is a threefold increase in the intracellular levels of magnesium during global ischemia.

After hospitalisation approximately thirty per cent of patients with acute myocardial infarction have hypomagnesemia and it may play a role in the development of hyperexitability of the myocardial tissue. (33,34,35).

The cause of this is proposed to be enhanced lipolysis that occurs in patients of acute myocardial infarction, caused by an excess of circulating catecholamines. This increases the free fatty acid levels in blood. They form complexes with the magnesium ions. This is followed by the deposition of “Mg2+ soaps” in the fat cells. (35)

There is epidemiological data suggesting that the incidence of coronary heart disease is higher in the areas where the soil is deficient in magnesium and also in area where the drinking water is soft. There is also consensus that reduced magnesium content in potable drinking water is linked with increased rates of Sudden cardiac deaths.

Electrophysiological Effects of Magnesium

The functions of Magnesium and potassium are very closely related. (36,37). Potassium loss is almost invariably associated with magnesium depletion. Hypomagnesemia is present in 40 per cent of the disease conditions involving low potassium levels in blood. (36). Hypopotassemia can only be corrected if magnesium is administered simultaneously with potassium. (37,38)

Electropharmacological effects of magnesium were identified experiments on isolated individual cardiac fibres and isolated cells with different types of in vitro techniques. The most noteworthy effects of magnesium are those which are exerted on potassium conductance and repolarising potassium currents. (30,35). Of all the potassium currents recognised, potassium has a tendency to flow into the cell cytoplasm rather than flow outwards into the extracellular fluid. This is because intracellular magnesium is a potent blocker of cardiac potassium channels. If there is an electrochemical gradient that favours outward flow of potassium,

magnesium ions blocks the potassium channel preventing the outward flow of potassium. Thus potassium channels acquire the property known as inward rectification. It is very important in maintaining the plateau of the action potential generated in the cardiac cells. (27).

Magnesium influences the slow inflow of calcium ions through the L-type of calcium channels. It is also a modulator of intracellular calcium in the sarcoplasmic reticular system. (36). When there is an increase or decrease of magnesium ion levels within the physiological limits, there is a corresponding inhibition or enhancement of the calcium inflow(I Ca). Thus magnesium regulates the calcium channel function and regulates the trans membrane calcium inflow. (27).

The cardiac cells of the nodal regions (Atrioventricular node, Sinoatrial node), have a characteristic calcium dependent depolarising mechanism. It is of a "slow response type". As magnesium blocks the inflow of calcium ions it plays an important role in controlling these nodal regions.

Magnesium can be considered as "nature's physiological calcium channel blocker". Even though this statement is apparently simplistic, it can be considered to be essentially true. (36)

It is also an important fact that the sarcolemma is permeable to magnesium. But the mechanism by which magnesium enters the cell through a supposed magnesium channel and how it gets removed from the cell through a sodium-magnesium exchange trans-membrane protein are not clearly identified. (27).

It can be considered that the anti-arrhythmic action of magnesium is much more complex than previously considered. The conductance of calcium and potassium in the cell membrane are all controlled and influenced by magnesium. It also regulates the Calcium flux at the level of the sarcoplasmic reticulum.

Arrhythmia mechanisms suppressible by magnesium

The established mechanisms of arrhythmia generation were re-entry and automaticity. The third mechanism that plays an important role in arrhythmia production and propagation is afterdepolarizations leading to triggered activity. Afterdepolarisations occur during the course of repolarisation. These are called as early afterdepolarisations or EAD's. (39). If afterdepolarisations occur after the action potential is completed, that is during phase 4 of the action potential, they are called as delayed afterdepolarisations. (DAD).

Recent experiments are highly indicative that, early afterdepolaristions and delayed afterdepolarisations and the triggered rhythms caused by them can be stopped by magnesium. The tachycardias caused by this phenomenon can be

terminated by addition of magnesium in in-vitro experimental studies. (41). Injection in-vivo also suppresses these mechanisms.

This is true despite the mechanisms behind early afterdepolarizations and delayed after depolarisations are different. EAD is caused by enhanced calcium inflow through the L type of calcium channels. Contributory effects are also made by sodium ions flowing through the non-inactivating sodium channels. (40). The emergence of EAD is helped by a prolonged duration of the action potential. Early after depolarisations have been most commonly observed in the purkinje cells of the heart of mammals which has the longest duration of the action potential. It is also known as APD. (39).

EAD are caused primarily by certain substances that lengthen the duration of the action potential. Other risk factors include bradycardia or any pauses in the heart rhythm. Other compounds include drugs like quinidine, barium, aconite, Bay K 8644.

Magnesium extinguishes the early after depolarisation that occur during the phase 2 or plateau phase of the action potential. It accomplishes this by mainly inhibiting the inflow of calcium. But apart from this it also influences the EADs which arise during the phase 3 of membrane potentials which are more negative than -60 millivolts and are modulated by sodium currents. (41).

The typical example of the arrhythmia in clinical practice based on early afterdepolarisation is the pause dependent “torsade de pointes” ventricular tachycardia which is associated with a long QT interval which may be drug induced or toxin induced.

The Delayed afterdepolarisations can be thought of as a result of oscillations of the resting membrane potential of myocytes. These heart cells may be overloaded with calcium ions or they may have decreased conductivity to potassium ions. This leads to activation of a non-selective, inward, transient flow of cations. It also activates the Na+-Ca2+ exchanger. Delayed after depolarisations can be created artificially in cardiac preparations by catecholamines, digitalis toxicity, caffeine, theophylline, histamine, lysophosphatidylcholine. This DAD triggers the activity that is responsible for arrhythmias. This is suppressible by magnesium.

When there is a deficiency or excess of magnesium in the body, there are alterations in the ecg recordings. These are expressed primarily in the calcium dependent SA nodes and AV nodes. Myocardial depletion of magnesium enhances the automaticity of the sinus node. Supplementation with magnesium has a negative chronotropic effect. (42). Magnesium also prolongs the PR interval by its action on the AV node. It accomplishes this by lengthening the Atrioventricular nodal refractory period. Magnesium does not seem to have significant actions on

the His-purkinje conducting system. Magnesium does not increase the refractory period of the atrial myocardium or the ventricular myocardium.

Electrocardiographic changes in magnesium deficiency include ST segment depression, flattening of T wave and QT prolongation. It is difficult to say if it is a direct effect of magnesium inadequacy or due to a co-existing hypopotassemia.

When there is hypermagnesemia, there is bradycardia, as a result of negative ionotropic action. There is prolongation of the PR interval. There may be intraventricular conduction abnormalities. The QRS complex is widened. The T waves are sharper and higher.

Treatment of arrhythmias of the heart with magnesium

Many of the arrhythmias of the heart can effectively and successfully treated with an appropriate dose of I.V magnesium chloride or magnesium Sulphate. This anti arrhythmic effect was reported first by Zwillinger in 1935. Eight patients were administered I.V magnesium sulphate for ventricular tachycardia caused by digitalis toxicity. Sinus rhythm was successfully attained in all these patients. Hypomagnemia (nineteen per cent) is more common than hypokalemia (ten per cent) in patients that are treated with digitalis and digitalis preparations. The

Sensitivity of the myocardial fibres to cardiac glycosides is also increased in the cardiac myocytes because of intracellular depletion of magnesium ions.

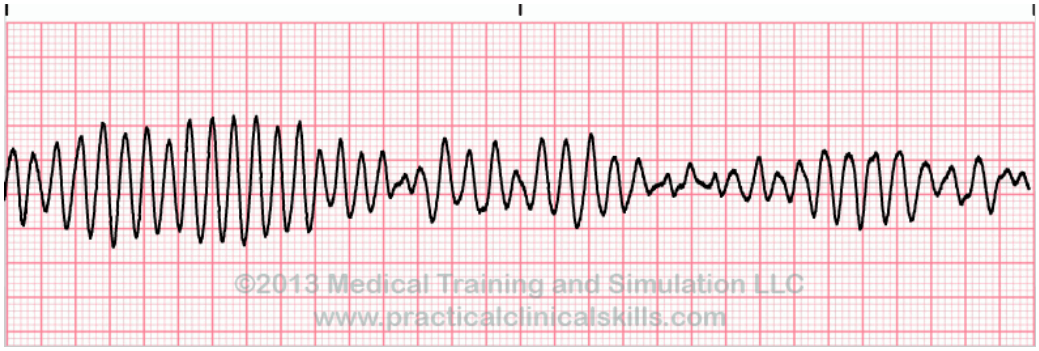
Ouabain- induced sustainable monomorphic ventricular tachycardia can be terminated by flunarazine which is a calcium overload inhibitor. It can also be inhibited by magnesium.

It was believed for a long time that the cause for this protective action was because of the reactivation of the digitalis blocked sodium potassium ATP ase pump in the sarcolemma. Later studies proved that Magnesium does not increase the activity of this enzyme. Instead of this, it exerts a direct effect in the membranes and modulates the outflow of potassium and cellular loss of potassium in the presence of digitalis.

Another arrhythmia in which magnesium is invaluable as a treatment modality is the treatment of polymorphic ventricular tachycardia or torsades de pointes. This arrhythmia often accompanies the long QT syndromes. This ventricular tachycardia is peculiarly bradycardia dependent. It is refractory to most other anti-arrhythmic therapy. As a matter of fact it may even be induced by other anti- arrhythmic drugs. The commonest drugs are the Class Ia or Class III drugs.

The first reports of successful therapy of this arrhythmia with magnesium were reported during the early 1980s. At this time its mechanism of action was not known widely or not at all.

Torsades de pointes can very often be terminated by Intravenous magnesium, especially when the QT interval has not yet been significantly shortened or if the QT interval is only shortened to a very small extent. (43).



Intravenous magnesium was also found to be proven useful in the treatment of barium and organophospherous compound - pesticide induced arrhythmias in the clinical as well as in the experimental setting.

The initial dose of magnesium(Mg^{2+}) is 1-2 grams. It is given as an I.V bolus during 1-2 minutes.. It can be repeated within 15 minutes. It is followed by a maintenance dose of 3mg-20mg/minute infusion for 6 hours to two days. Maintenance dose is necessary as it has a very fast renal elimination.

Arrhythmias suppressible by I.V MgSo4

Proven Use:

“Torsade de pointes” Ventricular Tachycardia

Digitalis toxicity-induced tachycardias

Magnesium deficiency-induced atrial fibrillation

Accepted use:

Ventricular extrasystoles/VT associated with Myocardial Infarction.

Multifocal atrial tachycardia

Investigational:

Re-entrant supraventricular tachycardias

Arrhythmias in mitral valve prolapse.

Sustained monomorphic Ventricular Tachycardia.

Postischemic/reperfusion arrhythmias

In the early stages of Myocardial infarction, there is transient hypomagnesemia, which may last for up to 48 hours. Abraham *et al*. performed a placebo-controlled, double-blind study on ECG that was continuously monitored in myocardial infarction patients, and found that the incidence of complicated ventricular arrhythmias was lesser in those patients treated with magnesium, than in the placebo-treated group. Rasmussen *et al.* administered magnesium ions on the second. The proportion of arrhythmias in group treated with magnesium was 21% and in the placebo group was 47%.

LIMIT 2 (Leicester Intravenous Magnesium trial) confirmed the above studies. But the ISIS-4 trial showed no benefit in using magnesium during the treatment of acute myocardial infarction. However in ISIS-4 trial, magnesium was administered after the administration of fibrinolytic therapy.

Magnesium ions can terminate post Myocardial infarction sustained monomorphic Ventricular tachycardia. Allen *et all.* reported that intravenous Magnesium Sulphate stops sustained monomorphic ventricular tachycardia accompanying organic heart disease. (44).

Intravenous magnesium is recommended in atrial fibrillation associated with alcoholic disease forms like holiday heart syndrome and atrial fibrillation seen in delirium tremens. (36). Prophylaxis with magnesium was found to be useful in the

prevention of atrial fibrillation in post-operative patients of coronary artery bypass grafting.

Intravenous Magnesium can be applied effectively in re-entrant supraventricular tachycardia) using an AV nodal circuit or using an AV accessory pathway. The verapamil like effect of intravenous magnesium upon the atrioventricular node in Supraventricular tachycardia is in accordance with the calcium antagonistic activity of magnesium ions. Magnesium also has parasympathtomimetic and antiadrenergic actions of magnesium. However, intravenous magnesium sulphate is less effective than adenosine or adenosine triphosphate in stopping supraventricular tachycardias. The side effects like nausea, flushing and headache are relatively more severe after the use of magnesium. So in the current setting magnesium sulphate has little role in the clinical management of supraventricular tachycardia.

Magnesium deficiency most likely plays an important role in the development of the hyperexcitability of neuromuscular connections frequently seen in the syndrome of idiopathic mitral valve prolapse. Magnesium therefore has an important place in preventing cardiac arrhythmias that are associated with **mitral** valve prolapse, partly due to its pharmacodynamic action and partly for the purpose of substitution to eliminate any hidden tetany. In this area, further investigations **are** required and more experience must be attained.

Materials and methods

Type of study: Case control study.

The study population:

Male patients who presented to Intensive Coronary Care Unit and were diagnosed as acute ST segment myocardial infarction.

The control population:

The group consisted of random young male population with no history of any significant illness the recent or remote past.

Total number of cases: 70

Total number of controls: 30

The cases were divided into three subgroups. The division was according to the age of the patient.

1. Subgroup A: Age less than 45 years

2. Subgroup B: Age between 45 to 55 years
3. Subgroup C: Age more than 55 years

Diagnosis and the investigation of the cases:

Diagnosis:

Patients, who came to the Intensive coronary care unit with symptoms suggestive of acute myocardial infarction, were evaluated.

A thorough history was elicited from the patient and the relevant clinical examination was performed.

A standard twelve lead Electrocardiogram was done in all of those patients. The ECG was analysed for the presence of acute ST elevation Myocardial infarction.

ECG criteria for diagnosing STEMI:

- New onset ST segment elevation more than 1millimeter in limb leads and/or more than 2 millimetre in precordial leads.
- There ST segment elevation should be present in two or more leads.
- The two or more leads should be contiguous with respect to each other.

After the interpretation of ECG the patients were planned to be included in the study population if they fulfilled the ECG criteria for STEMI, if they satisfied the additional inclusion criteria for the cases and if they did not fall into the exclusion criteria.

Inclusion criteria:

- Male patients.
- Patients who has symptoms of acute myocardial infarction.
- Patients who satisfy the ECG criteria for diagnosis of acute STEMI.
- Patients who presented within twelve hours after the onset of symptoms.
- Patients who consented for being included in the study.

Exclusion criteria

- Female patients
- Patients with previous history of ischemic heart disease
- Patients with previous history of hypertension
- Patients with previous history of diabetes mellitus.
- Patients with previous history of dyslipidemia.
- Patients who are on medications like diuretics for any disease conditions.

Procedure done

1. Obtaining informed consent from the patient for the study
2. Approximately 4 ml of venous blood was collected from the patient.
3. The time interval between admission and the drawing of blood did not exceed 6 hours.
4. The blood drawn was transferred to plain blood collection bottle without any anticoagulants.
5. Appropriate labelling was done.
6. The Performa for each individual case was filled promptly as soon as the above steps were being undertaken.
7. The blood collected was send to the biochemistry laboratory.
8. The blood soon separated into the serum and the fibrin clot.
9. The blood was centrifuged at 2000 rpm for complete separation of the serum from the blood.
10. The serum thus obtained was estimated for its magnesium concentration using colorimetric method.

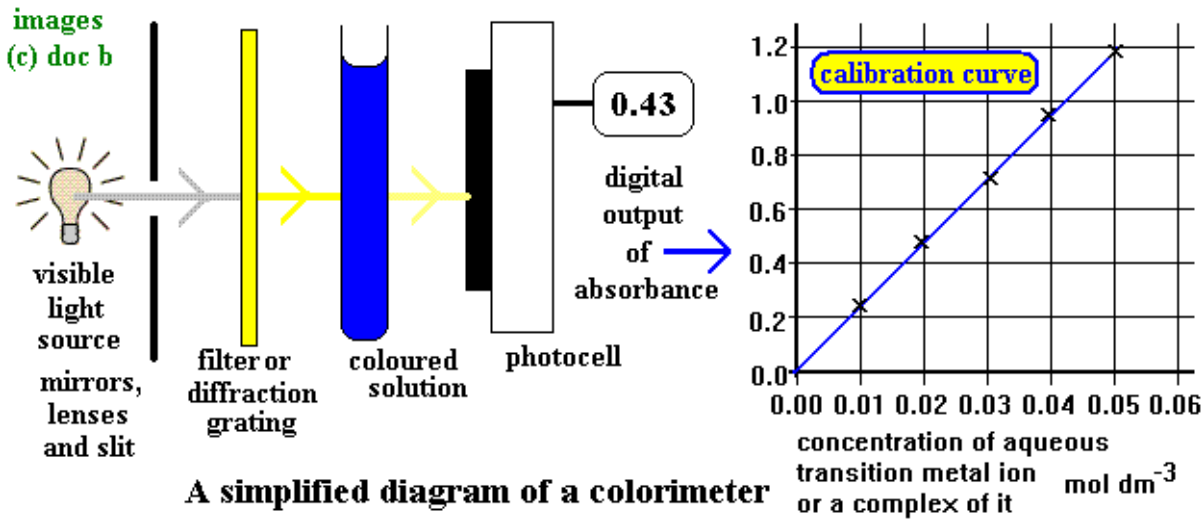
A total of seventy cases who met the inclusion criteria were investigated for serum magnesium levels over a period that extended from October 2013 to August 2014.

Method for magnesium estimation

Colorimetry

It is the technique used to determine the concentration of coloured solutes in a solution.

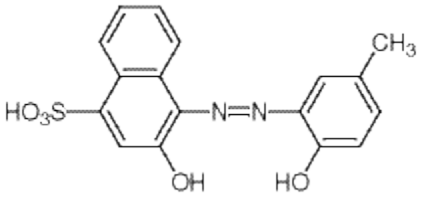
A light of known wavelength and intensity is passed through the coloured solution. There is a change in the wavelength and maybe the intensity of the light beam after the light passes through the solution. This light and its properties are detected by a spectrophotometer. The change in the the property of light emitted and detected is proportional to the intensity of the colour in the solution. The intensity of the colour is directly proportional to the concentration of the solute. Thus, indirectly we can estimate the concentration of the dissolved compound.



A simplified diagram of a colorimeter

Calmagite Method

Calmagite is a complex chemical compound. It is wine red in colour when it is combined with a metal ion like Mg2+ and blue in colour when it is not combined with a metal ion.



Principle:

Magnesium combines with Calmagite in an alkaline medium to form a red coloured complex. Interference by calcium and proteins is eliminated by the addition of specific chelating agents and detergents. The intensity of the colour formed is directly proportional to the amount of magnesium present in the sample.

Magnesium + Calmagite $\xrightarrow{\text{Alkaline Medium}}$ Red coloured complex.

Normal reference values:

Serum (Children) : 1.5 – 2.0 mg/dL

(Adults) : 1.5 to 2.5 mg/dL

CSF :2.0 to 3.0 mEq/dL

Urine :6.0 to 8.5 mEq/dL

Sample material:

Serum that is free from haemolysis. Magnesium is reported to be stable in serum/plasma for 7 days at 2-8 degree celcius.

Procedure:

Wavelength/filter: 510 nm (Hg 546nm)/Green.

Temperature: Room temperature.

Light Path: 1 centimetre.

Incubation time: 5 minutes.

Linearity:

The procedure is linear upto 10mEq/L. If Values exeed this limit, dilute the sample with distilled water and repeat the assay. Calculate the value using an appropriate dilution factor.

Calculations:

Magnesium in mEq/L = (Abs.T/ Abs.S) x 2

2 mEq/L =2.44md/dl.

Data collection and analysis

When the case is selected to be included in the study, the Performa is filled out for each case. The Performa contains important information like the age of the patient, duration of symptoms, time interval between hospital administration and sample collection, the severity of myocardial infarction, and the follow up details of the patient for his duration of hospital stay.

The entire data is tabulated and analysed. The information we are looking for is the presence and prevalence of hypomagnesemia in the study population. If it

is prevalent we use various statistical methods to determine if the prevalence level can be considered significant or not.

We also compare the mean blood magnesium levels of the study population and the control population. If there is any difference between the mean magnesium levels, we try to determine if the difference is statistically significant by calculating the P value for the data set.

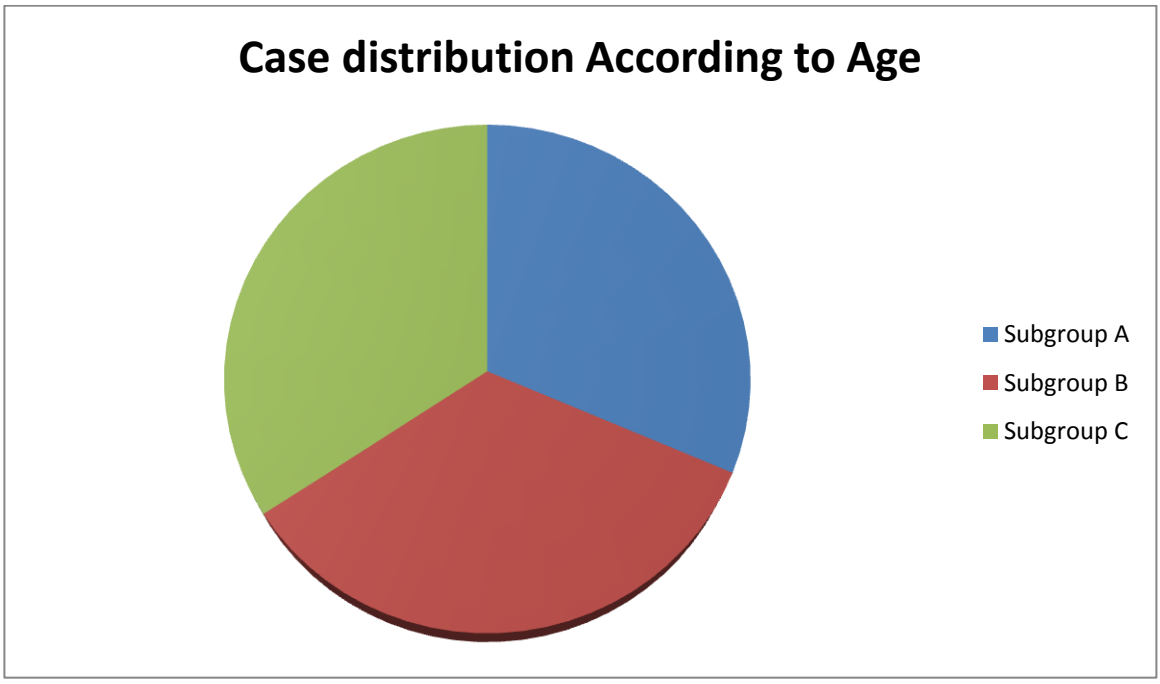
After obtaining the results, we shall compare the observations and results with previous studies of similar nature which have been published in popular medical journals. We look if there is an agreement between my study and the previous studies. If there is no agreement we shall make an attempt to discuss the reasons for the difference in outcome.

Observations and results.

Total Number of cases =70

Total number of controls = 30

- Subgroup A (Age<45)
- Subgroup B (Age45-55)
- Sub group C (Age >55)

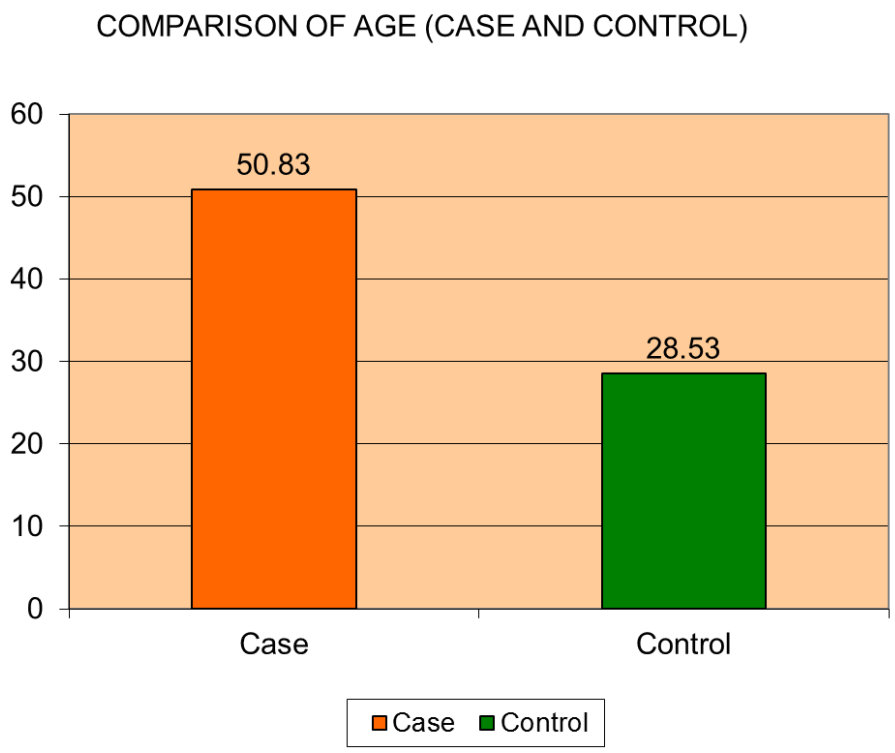


- Subgroup A n=22
- Subgroup B n=24
- Subgroup C n=24

Age comparison

Mean Age of the cases = 50.83

Mean Age of the control group = 28.53



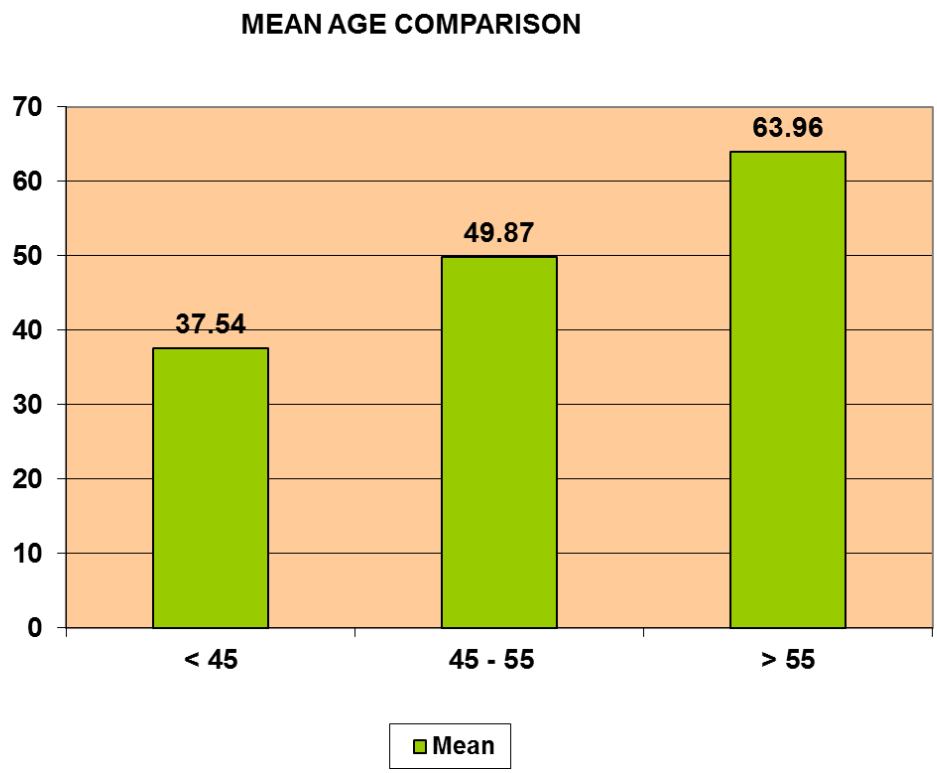
- The control group were considerably from a younger population.
- The cases generally belonged to the middle age as myocardial infarction occurring for the first time is essentially more common in that group

Mean age of the Subgroups.

Subgroup A- 37.5

Subgroup B-49.87

Subgroup C-63.96



- Within the subgroups, the cases were distributed favourably and there was homogeneity in distribution.
- There was no clustering of cases towards a specific age group.

Prevalence of hypomagnesemia in the study population

Defining Hypomagnesemia: Cases who have a serum magnesium levels of less than 1.5milligrams per one hundred millilitres (<1.5mg/100ml) of blood.

Total number of cases =70

Total number of cases with hypomagnesenia = 1

Patient name - Murugan

Age 38 -years

Diagnosis – Acute inferior wall ST elevation myocardial infarction.

Serum Magnesium Levels – 1.2mg/100 ml.

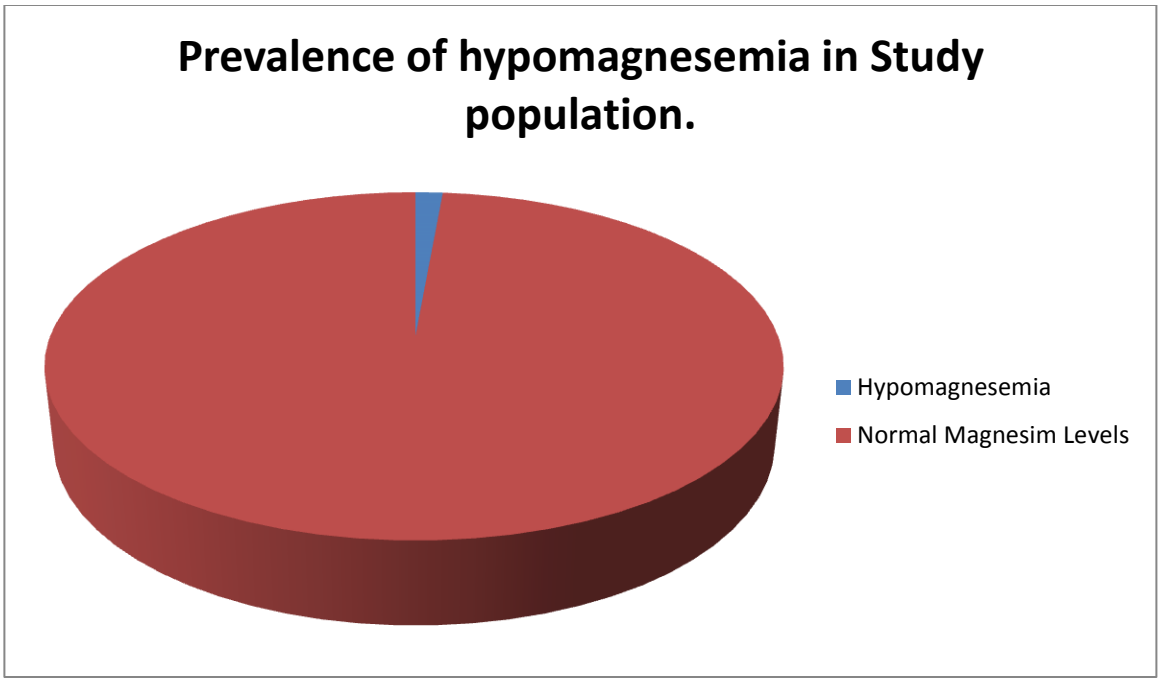
Outcome –No immediate or long term complications.

Prevalence of Mypomagnesemia in the Study population

$$= \frac{\text{Number of patients with hypomagnesemia}}{\text{Total number of cases}} \times \mathbf{100}$$

$$= \frac{1 \times 100}{70}$$

= **1.42 %**



Prevalence of hypomagnesemia = 1.42 %

Significance of the finding

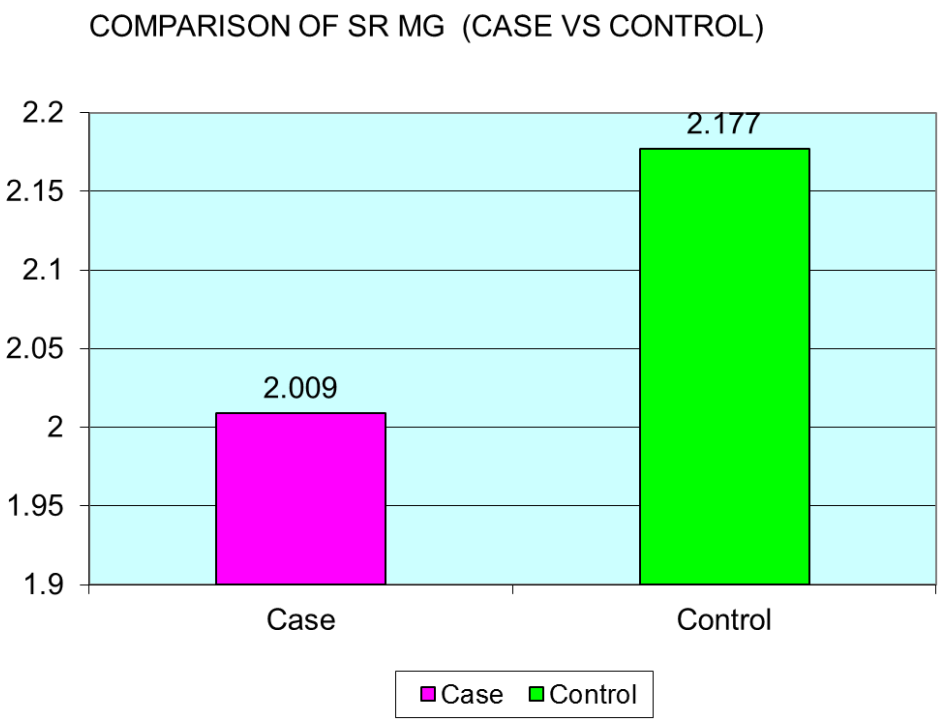
- Magnesium is **normally** distributed in the general population.
- The "normal levels" of magnesium (1.5-2.5 mg/dl) apply only to the population that lie inside two standard deviations from the mean, or to the population that lies within 95% confidence interval.
- If the prevalence is significant, it must be more than 5%.

Conclusion: The prevalence of hypomagnesemia in the sample population is **not significant.**

Mean levels of Magnesium in the cases and controls.

Cases(n=70) : 2.009

Controls(n=30) : 2.177



As the above data and bar diagram depicts, the mean levels of magnesium is lower in the acute myocardial infarction patients, when compared to the healthy young control population.

Now we shall see if the above difference is statistically significant.

Sr. Mg for Case and Control

	Mean	SD	p' value	
Case	2.009	0.303	0.013	Significant
Control	2.177	0.311		

Mean value of the cases = 2.009

Mean value of the controls = 2.177

Diffeence between the means = **0.168**

Standard deviation of the cases = 0.303

Standard Deviation of the controls = 0.311

Standard error of difference between the two means

$$= \sqrt{\frac{(SD1)^2}{n1} + \frac{(SD2)^2}{n2}}$$

$$= \sqrt{0.0013 + 0.0032}$$

Standard error of difference between the two means = 0. 067.

If the result is significant, two times the standard error of difference between the two means will be less than the actual difference between the two means.

So, 2 X Std. error of difference = A= 2X0.067 = 0.134

Difference between the means = B = 0.168

So, A< B,

So the difference is significant

Conclusion.:

The mean levels of serum magnesium in acute myocardial infarction patients at the time of admission is significantly lower than that of the control population.

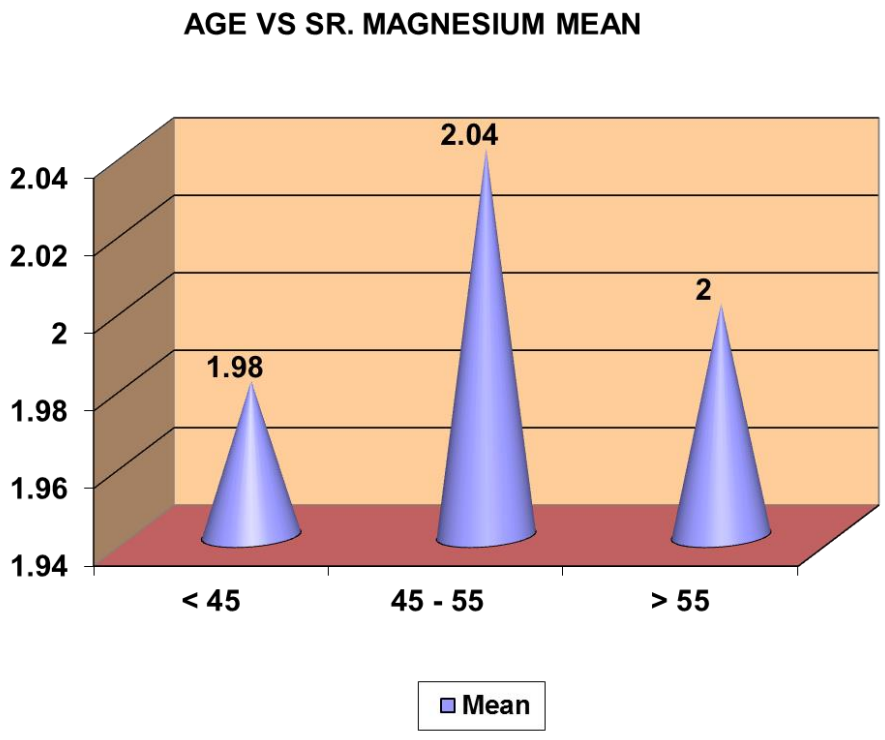
Comparison between the various subgroups.

Mean value of Serum Magnesium levels:

Subgroup A- 1.98 mg/100 ml

Subgroup B – 2.04 mg/100ml

Subgroup C –2.00 mg/100 ml



Tests for significance:

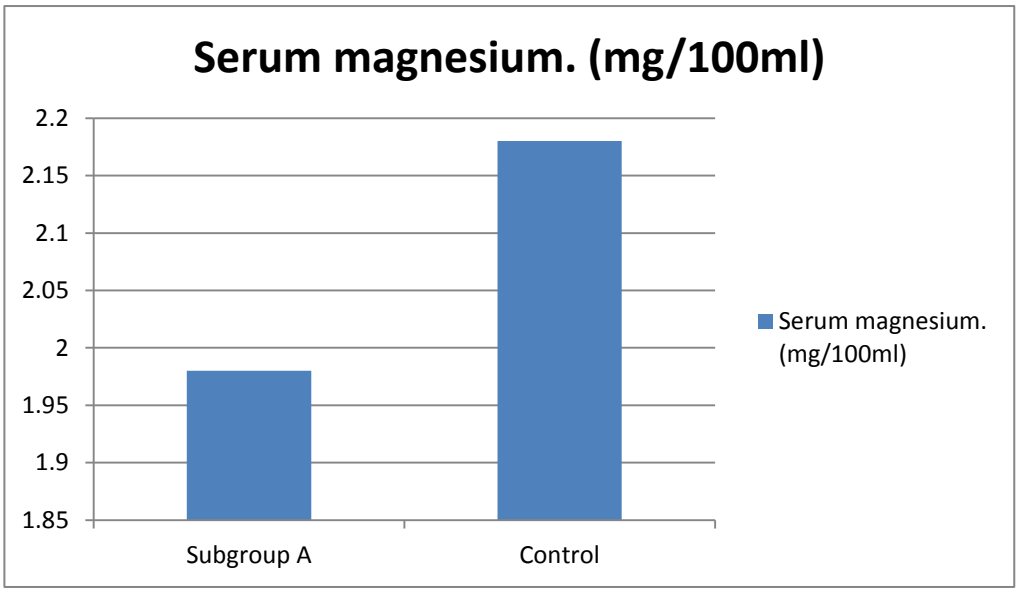
Tabular column

Sr.Mg	Mean	SD	p value	
< 45	1.98	0.35	<0.01	Significant
45 – 55	2.04	0.31	0.83	Not significant
> 55	2	0.26	<0.01	Significant.

- Subgroup A had significantly low levels of mean magnesium levels when compared to the controls
- Subgroup B had lower levels of mean magnesium levels but it was not statistically significant
- Subgroup C had significantly lower levels of magnesium levels when compared to the control group

Subgroup A – mean =1.98

Control group- mean = 2.18



Difference between the two means = 2.18 – 1.98 = 0.2 mg/dl (B)

Standard error of difference between the two means = 0.09 mg/dl (A)

If the result is significant, two times the standard error of difference between the two means will be less than the actual difference between the two means

So,

2 X (Std. error of difference) = 2X A = 0.18 mg/dl

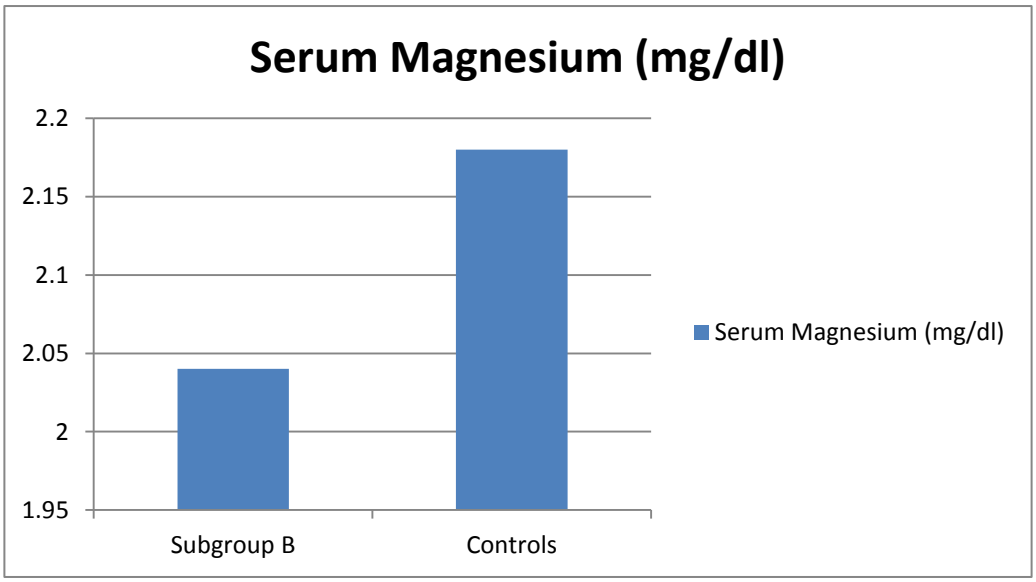
Difference between the means = 0.2 mg/dl.

[0.18is less than 0.2]

Conclusion: The difference is statistically significant.

Subgroup B – mean = 2.04

Control group –mean = 2.18



Difference between the two means = 2.18 – 2.04 = 0.14 mg/dl (B)

Standard error of difference between the two means = 0.085 mg/dl (A)

If the result is significant, two times the standard error of difference between the two means will be less than the actual difference between the two means

So,

2 X (Std. error of difference) = 2X A = 0.17 mg/dl

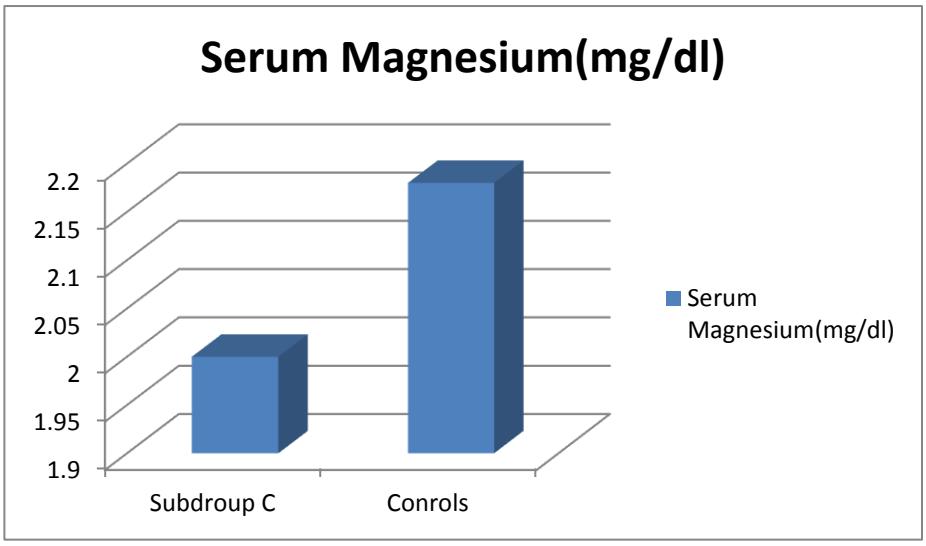
Difference between the means = 0.14 mg/dl.

[0.17 is not less than 0.2]

Conclusion: The difference is **NOT** statistically significant.

Subgroup C – mean = 2.0

Control group – mean = 2.18



Difference between the two means = 2.18 – 2.00 = 0.18 mg/dl (B)

Standard error of difference between the two means = 0.077 mg/dl (A)

If the result is significant, two times the standard error of difference between the two means will be less than the actual difference between the two means

So,

2 X (Std. error of difference) = 2X A = 0.154 mg/dl

Difference between the means = 0.18 mg/dl.

[0.154 is less than 0.18]

Conclusion: The difference **is** statistically significant.

Discussion

Strengths and weaknesses of the study design

Strengths

1. The ease of defining the study population- The diagnosis of ST segment myocardial infarction is relatively simple
2. Reduction of confounding factors: The study population was relatively homogenous. None of the patients had previous history of coronary heart disease. None of them had any treatment with diuretics which could drastically alter the serum magnesium levels. Furthermore the study population were not also known cases of diabetes mellitus or hypertension which can also have an effect on the results.
3. The relative ease of the procedure performed: Patient is not put through any additional difficulty to be a part of this study. The blood samples taken for the test were mostly from a portion of the blood sample taken for routine investigations .
4. The objective nature of the result obtained: The result obtained is the concentration of magnesium ions in the blood of the patients. There is no need for questionnaires. The result is not influenced by the subjective variation of neither the patient nor of that of the examiner.

Weaknesses

1. Relatively Small size of the study population: The number of cases decided to be included in the study was 70. The number of controls was 30. This study was completed over a period of twelve months. The inclusion criteria was stringent. It was difficult to find out a case of myocardial infarction without the frequent co-morbid conditions of hypertension and diabetes. As the number of cases decreases, more the sample becomes non representative of the general population.
2. Variation in time interval of collecting sample: All of the samples were collected within six hours of admission into the hospital. Even though the time interval is relatively short, the internal environment of the patient in that acute condition can vary significantly, especially regarding the circulating catecholamine levels, thus affecting the magnesium content.
3. Some samples were collected after fibrinolytic therapy: In our institution, the door to needle time of one hour is strictly adhered to. As previously mentioned, the time interval within the sample was upto six hours. So, the action of the fibrinolytic therapy can also affect the levels of magnesium in the blood, as the primary pathological mechanism is reversed. But to look on the positive side, in all these patients, myocardial necrosis was universal

according to the definition. Thus, a high degree of homogeneity was still preserved.

Previous Studies

Before we dive into the discussion of the results obtained, let us review the results and conclusion of previous studies on this topic of serum magnesium levels in acute myocardial infarction patients.

1. S**erum magnesium in Acute Myocardial infarction**: Acta Medica Scandinavia. Volume 206, Issue 1-6 pages 59-66, December 1980.

   -Thomas Dyckner

   During the one and a half years of the study, 342 patients with acute myocardial infarction were treated at Serafimerlasarettet. The Acute MI group had significantly lower serum magnesium levels than a reference group. The incidence of Ventricular ectopics, Ventricular tachycardias and Ventricular fibrillation were significantly higher in the hypomagnesemic patients.

2. **Magnesium and Acute Myocardial Infarction.Transient Hypomagnesemia Not Induced by Renal Magnesium Loss.** *Arch Intern Med.* 1986;146(5):872-874.

H. Sandvad Rasmussen, MD; P. Aurup, MD; S. Hojberg, MD

Blood and urine samples were taken during the time of admission. Urine samples were taken every 8 hours for the next 7 days. Both urine and blood magnesium were analysed. 13 patients were found to have MI. 11 normal people were taken as controls. The acute myocardial Infarction patients had significantly lower levels of serum magnesium. The urine concentration of magnesium did not increase with time. This shows that the hypomagnesemia is not due to the renal loss of magnesium. The mechanism is due to a shift from the extracellular compartment. Maybe due to sequestration with the increased levels of free fatty acids.

3. **Serum Magnesium and Potassium in Acute Myocardial Infarction.**
Arch Intern Med. 1987;147(3):465-469.
-Henryk Kafka, MD; Lorrie Langevin, RN.

Over a period of 13 months, serum magnesium and potassium levels were measured in 590 patients admitted in a coronary care unit. Hypokalemia occurred in 17% of the patients. However hypomagnesemia occurred in only 4% of the studied group. However it was still a higher incidence than the reference population. Ventricular arrhythmias occurred in ten of the thirteen patients with myocardial infarction and hypomagnesemia. However the mean levels of serum magnesium levels in the normal healthy population was significantly

higher than the reference levels. So the findings in this study may not be applicable to outside population because of higher magnesium content of soil in the selected study area of south eastern Ontario.

So in most of the studies conducted above, there is enough evidence to state that there is transient hypomagnesemia in acute myocardial infarction patients. Reference of literature also mentions that the incidence of hypomagnesemia in acute myocardial infarction may be upto 30%.(29).

In this study, the prevalence of hypomagnesemia in the studied cases was very low to be of any significance. The patient who developed hypomagnesemia did not develop any short term or long term complications. . However the mean serum magnesium levels of the cases were significantly lower than that of the control population.

So this study does not agree with most of the studies conducted previously regarding the significant prevalence of hypomagnesemia in acute MI patients.

The reasons for this result obtained are not exactly clear. Some hypotheses could be put forward. Some of them are given below.

1. <u>Increased levels of magnesium ions in the water supply of the study population:</u>

The population of Tirunelveli district and the neighbouring districts in Tamil Nadu are relatively arid regions. The supply of drinking water is largely from the ground water. The ground water is obtained by means of bore wells. The water thus obtained is mainly hard water. Hard water contains increased levels of magnesium ions when compared to hard water.

Hard water is water that has high mineral . Hard water is formed when water percolates through deposits of calcium and magnesium-containing minerals such as limestone, chalk and dolomite. Hard water is not a health hazard.

Soft water contains 0-20 mg/L of $MgCO_3$ while hard water may contain upto 60-180 mg/L of $MgCO_3$.

The mean magnesium levels of the control population are also higher than the mean levels of magnesium levels in the general population. This may be an evidence to support this hypothesis.

2. <u>Increased magnesium intake through diet.</u>

The richest sources of magnesium in diet are legumes, beans and green leafy vegetables. They contain about 500mg/ kilogram of magnesium. Indian diet, when compared to western diet is relatively richer in green leafy vegetables and legumes. Most of the studies were performed on western population.

This may account for the slightly increased mean magnesium levels in controls when compared to the general population.

3. Genetic variability in the study population.

The study population that mainly consisted of south Indians are constitutionally different from the Caucasians and black populations in which most of the western studies were conducted. In such a population group, the magnesium homeostasis may be different from western population. Although this is a remote possibility, we should keep this in the back of our minds, especially when we know the difference in clinical profile of acute MI patients of South Asia and the western population.

Summary

A total of 70 cases of Acute Myocardial infarction patients who presented to ICCU in Tirunelveli Medical College during the time period of August 2013 to September 2014 were studied for their magnesium levels at the time of presentation. Blood samples were collected within 6 hours of admission. They were monitored during their duration of admission for any complications.

The study population was divided into three subgroups according to the age of the patients. 30 young healthy individuals were taken as the control group.

The magnesium levels were measured using colorimetric method with calmagite being the reagent used.

On analysis of the data, the prevalence of hypomagnesaemia in the study population was not significant.

The mean serum magnesium level of the study population was significantly lower than that of the control population. (2.009 mg/dl vs 2.177mg/dl)

There were also significantly low magnesium levels in two of the three subgroups, when compared to the controls. The age group from 45 to 55 had lower levels of mean magnesium levels, but it was not statistically significant.

Conclusion

The prevalence of hypomagnesemia in the study population was not significant. However the mean serum magnesium levels in the study population as a whole was significantly lower than that of the control group. The reduction in magnesium levels were not statistically significant in one of the three subgroups whose age group was 45-55 years.

This is in concordance with previous studies on this topic. Magnesium levels do fall significantly in Acute myocardial infarction patients. However in this study the fall in magnesium is not high enough to cause hypomagnesemia and result in any increase in complications.

The probable cause for this result may be due to the high magnesium content of the drinking water (Hard Water) in the area in an around Tirunelveli district. More such studies are needed especially with a bigger sample size to find out if the current results are reproducible or not.

Bibliography

1. World Health organisation: The global burden of disease:2004 update.

2. Lopez AD, Mathers CD, Ezzazi et al: Global burden of disease and risk factors,2006,p 552

3 Balbinotto Neto G, Silva EN: The costs of cardiovascular disease in Brazil. Arq Bras Cardiol 91:198 2008

4 Wild S Roglic G, Green A et al: Global prevalence of diabetes. Diabetes care 27:1047,2004

5 Fung TT, Malik V, Rexrode KM, et al: Sweetened beverage consumption and risk of coronary heart disease in women. Am J Clin Nutr 89:1037,2009

6 Harrissons Principles of internal Medicine, 18 th Edition.
Pages 1798 - 2082

7 Braunwald's Heart Disease. 9th edition. Bonow, Mann, Zipes, Libby Pages 1049 - 1258

8 Davidson's Principles and practice of Medicine. 20th edition. Pages 591-600.

9 Wu KC: fighting the fire of myocardial reperfusion injury: How to define success? J Am Coll Cardioll 53:730,2009

10 Kawasaki ,T Akakabe Y, Yamano M, et al : Vagal enhancement as evidence of residual ischemia after inferior myocardial infarction. Pacing Clin Electrophysiol 32:52,2009.

11. Heaton, F.W. 1976. Magnesium in intermediary metabolism. In: *Magnesium in Health and Disease*. Canatin M., Seelig, M. eds. p 43-55. New York. SP Medical and Scientific Books.

12 Webster, P.O. 1987. Magnesium. *Am. J. Clin. Nutr.*, 45: 1305-1312.

13. Breibart, S., Lee, J.S., McCoord, A. & Forbes, G. 1960. Relation of age to radiomagnesium in bone. *Proc. Soc. Exp. Biol. Med.*, 105: 361-363.

14 Waterlow, J.C. 1992. *Protein Energy Malnutrition*. London, Edwin Arnold.

15. Al-Ghamdi, S.M., Cameron, E.C. & Sutton, R.A. 1994. Magnesium deficiency: pathophysiologic and clinical overview. *Am. J. Kidney Dis.*, 24: 737-754.

16. Rude, K.K. & Olerich, M. 1996. Magnesium deficiency: possible role in osteoporosis associated with gluten-sensitive enteropathy. *Osteoporos. Int.*, 6: 453-461.

17. Abrams, S.A., Grusak, M.A., Stuff, J. & O'Brien, K.O. 1997. Calcium and magnesium balance in 9-14 year old children. *Am. J. Clin. Nutr.,* 66: 1172-1177.

18. Sojka, J., Wastney, M., Abrams, S., Lewis, S.F., Martin, B., Weaver, C. & Peacock, M. 1997. Magnesium kinetics in adolescent girls determined using stable isotopes: effects of high and low calcium intakes. *Am. J. Physiol.,* 273-42: R710-R715.

19. Greger, J.L., Smith, S.A. & Snedeker, S.M. 1981. Effect of dietary calcium and phosphorus magnesium, manganese and selenium in adult males. *Nutr. Res.,* 1: 315-325.

20. McCance, R.A. & Widdowson, E.M. 1942. Mineral metabolism on dephytinised bread. *J. Physiol.,* 101: 304-313.

21. Kelsay, J.L. Bahall, K.M. & Prather, E.S. 1979. Effect of fiber from fruit and vegetables on the metabolic responses of Human subjects. *Am. J. Clin. Nutr.,* 32: 1876-1880.

22. Hu, J-F., Zhao, X-H. Parpia, B. & Campbell, T.C. 1993. Dietary intakes and urinary excretion of calcium and acids: a cross-sectional study of women in China. *Am. J. Clin. Nutr.,* 58: 398-406.

23. Quarme, G.A. & Disks, J.H. 1986. The physiology of renal magnesium handling. *Renal Physiol.,* 9: 257-269.

24. Food and Nutrition Board, Institute of Medicine. 1997. *Dietary reference intakes for Calcium, Phosphorous, Magnesium, Vitamin D, and Flouride.*Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. Washington D.C., National Academy Press.

25. Shils, M.E. 1988. Manesium in health and disease. *Annu. Revs Nutr.,* 8: 429-460

26. Shils, M.E. 1969. . Experimental Human magnesium depletion. *Medicine,* 48: 61-85.

27. White RE, Hartzell HC Magnesium ions in cardiac function. Regulator of ion channels and second messengers. Biochem *Pharmacol*

38,859-867 (1989)

28. Garfinkel L, Altschuld RA, Garfinkel D: Magnesium in cardiac energy

metabolism. JMol Cell Cardiol18,1003-1013 (1986)

29. Ghani hF, Rabah M: Effect of magnesium chloride on electrical stability of the heart. *Am* Heart *J* 94,600-602 (1 977)

30. Matsuda H, Saigusa A, Irisawa H: Ohmic conductance through the inwardly rectifying K channel and blocking by internal Mg2+. Nature 325,156-159(1987)

31. DeCarli C, Sprouse G, LaRosa JC: Serum magnesium levels in symptomatic atrial fibrillation and their relation to rhythm control by intravenous digoxin. *Am J* Cardiol57,956-959 (1986)

32. Whang R, Whang DD, Ryan Mp: Refractory potassium repletion. A consequence of magnesium deficiency. *Arch* Intern Med 152, 40-45 (1992)

33. Rasmussen HS, Aurup P, Hojberg S, Jensen K, McNair P Magnesium and acute myocardial infarction. Transient hypomagnesemia not induced by renal magnesium loss in patients with acute myocardial infarction. *Arch* Intern Med 146,872-874 (1986)

34. Fazekas T, Vos M, Leunissen J, Gorgels A, Wellens HJJ Pharmacological

effects of magnesium and ethmozine on ouabain-induced

ventricular tachycardias in normomagnesemic conscious dogs with av block

35. Mink EB, Brick JE, Shane SR Alterations of long-chain free fatty acids and magnesium concentrations in acute myocardial infarction. *Arch* Intern Med 141,44143 (1981)

36. Iseri LT, Allen BJ, G i e l ML, Brodsky MA Ionic biology and ionic medicine in cardiac arrhythmias with particular reference to magnesium. *Am* Heat? *J* 123,1404-1409 (1992)

37. Rude RK: Physiology of magnesium metabolism and the important role of magnesium in potassium deficiency. *Am J* Cardiol63

38. Whang R, Whang DD, Ryan Mp: Refractory potassium repletion. A consequence of magnesium deficiency. *Arch* Intern Med 152,

39. January *CT*, Makielski JC: Triggered arrhythmias: New insights into basic mechanisms. *Curr* Opiriioti Curdiol5.6568 (1990)

40. Zipes DP Monophasic action potentials in the diagnosis of triggered arrhythmias. Pmg Cardiovmc Dis 33,385-3% (1991)

41. Kaseda S, Gilmour RF, Zipes DP Depressant effect of magnesium on early afterdepolarizations and triggered activity induced by cesium, quinidine, and 4-aminopyridine in canine cardiac Purkinje fibers. AmHeartJ118,45~(1989)

42. Gums JG: clinical significance of magnesium: A review. Drug *Intel1* Clin Pharm 2 I , 240-246 (1987)

43. Keren A, Tzivoni D: Magnesium therapy in ventricular arrhythmiasPACE 13,937-945 (1990)

44. Brooks R, McGovern BA, Chemow B, Garan H. Ruskin JM: Sup pression of monomorphic ventricular tachycardia by intravenous magnesium chloride predicts the effectiveness of oral calcium channel blocker therapy. *Circultrtion* 82 (suppl Ill), 82A (1990)

Proforma

Case No:

Name of the Patient:

Age:

Presenting Complaints:

Past History(Diabetes, Hypertension,CAD):

Drug History:

Personal History (Smoking, Alcohol):

General Examination:

Vitals:

Cardiovascular System:

Other System Examination:

ECG Findings:

Serum Magnesium Levels:

Follow up notes:

CONSENT: I, the undersigned agree voluntarily to be included in the study. I Understand that this is a minimal invasive procedure.The procedure is explained to me in my own words. I agree to give 5ml of blood for the investigation.

Date:

Place: Signature

Master Chart

Total Cases [n=70]			
Number	Name	Age	Serum Magnesium(mg/100ml)
1	Muthuramalingam	44	2.6
2	Subbiah	44	1.9
3	Murugan	41	1.9
4	Chelladurai	38	1.9
5	Mohammed Aboobakker	39	1.9
6	Murukan	38	**1.2**
7	Paramasivam	30	1.8
8	Jayatheswaram	40	2.1
9	Sivaraman	37	1.9
10	Appakkutty	35	1.8
11	Chinnasamy	35	1.8
12	Balakrishnan	28	2.1
13	Velmurugan	32	2.1
14	Shanmugam	30	3
15	Peer Mohammed	39	2.1
16	Shivadas	42	1.7
17	Krishnakumar	44	2.2
18	Arjun	44	2
19	Michael	33	2.3
20	Pandiraj	32	1.9
21	Ramiah	39	1.8
22	Arulraj	42	1.6
23	Palavesem	54	2.2
24	Vijayaraj	47	2.3
25	John Kennedy	50	2.5
26	Natchthiram	50	1.6
27	Velu	53	1.8
28	Suryanarayanan	46	2.6
29	Arunachalam	50	1.7
30	Pitchiah	52	1.8
31	Ramalingam	51	2.1
32	Selvaraj	54	2.1
33	Ramasamy	50	2.3

34	Jayasankar	45	2.5
35	Nadar Ali	45	1.9
36	Selvan	45	1.9
37	Abdul kathar	55	1.6
38	Ramanujan	49	2.3
39	Ayyadurai	53	1.9
40	Velayuthan	47	2
41	Jesudas	46	1.8
42	Palamimurigan	54	1.6
43	Venkatesh	50	2.4
44	Muthukumar	54	2.1
45	Shahjahan	46	1.7
46	Periyasamy	51	2.2
47	Muthu	56	1.6
48	Palavesam	61	1.9
49	Selvaraj	65	2
50	Thalavai	75	1.8
51	Victor	60	2.4
52	Natarajan	65	2.2
53	Shanmugavel	68	1.8
54	Eswaran	60	1.9
55	Moosha	57	1.9
56	Ramasamy	68	1.8
57	Ranganathan	61	1.6
58	Samuel	75	2.2
59	Mariappan	60	2.4
60	Vallinayakam	75	2
61	Manoharan	59	2.1
62	Pandaram	65	1.8
63	Esakkipandi	68	2
64	Hyder Ali	58	2.4
65	Ganeshan	57	1.7
66	Esakkiappan	72	1.9
67	Joseph	61	2.2
68	Murukan	63	2.3
69	Vishnudas	64	1.8
70	Palaniappan	62	2.4
	MEAN		2.01

Control [n=30]			
Number	Name	Age	Serum Magnesium (mg/100ml)
1	Benny	25	1.7
2	Venkatesh Raju	28	2.2
3	Raeez	26	2.3
4	Alex Mathew	27	2.5
5	Ayyadurai	66	1.5
6	Kalimuthu	22	2.3
7	Dileepan	23	2
8	Gomathy	22	2.2
9	Ankit	22	2.2
10	Anu	24	2.3
11	Kumar	30	2.3
12	Saravanan	26	2.1
13	Jered	27	2.1
14	Sayee Venkatesh	27	2.8
15	Arun Paulose	28	1.7
16	Jose Paikkada	28	2.2
17	Ibrahim Ali	34	2.4
18	Prasanna	30	2.7
19	Arun Kumar	27	1.9
20	Balachander	27	2.2
21	Balamarimuthu	24	1.8
22	Sriram	23	2.4
23	R Rajkumar	23	2.2
24	Hariharan	23	1.7
25	Krishna	22	1.9
26	Balamurugan	24	2.2
27	Chelladurai	55	2.6
28	Gopal	40	2
29	Vijay	26	2.3
30	Jithin Raj	27	2.6
	MEAN		2.18

Abbreviations

CVD- Cardiovascular disease

CHD-Coronary Heart Disease

IHD- Ischemic Heart Disease

CVA- Cerebrovascular Accident

MI – Myocardial Infarction

STEMI – ST segment elevation Myocardial infarctiom

NSTEMI- Non ST segment elevation Myocardial Infarction

Mg 2+ -Magnesium ions.

Ca2+ -Calcium ions.

K+ -Potassium ions

Na+ Sodium ions

VT – Ventricular Tachycardia

SVT- Supraventricular Ventricular Tachycardia

AF – Atrial Fibrillation

I.V – Intravenous

A.T.P Adenosine Tri Phosphate

cAMP –Cyclic Adenosine Monophosphate

NADPH- Nicotinamide Adenide Diphosphate Hydrogen

S.D – Standard Deviation.